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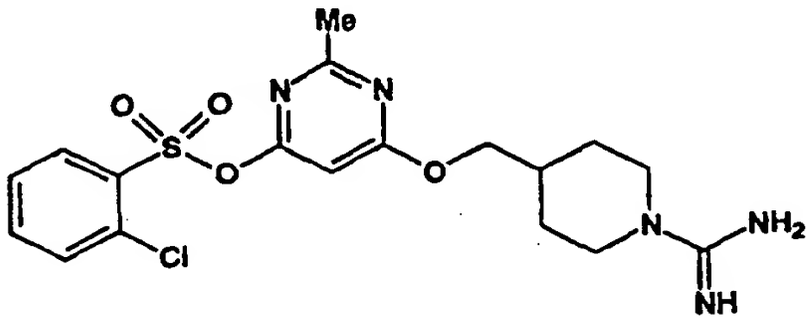
(54) Title: AMIDINO AND GUANIDINO HETEROCYCLIC PROTEASE INHIBITORS



(A)

(57) Abstract

Disclosed are amidino, amidinohydrazone and benzamidino compounds having a central heterocyclic core, of the general formula (R^1-Z-X-Y-W or solvates, hydrates or pharmaceutically acceptable salts thereof; wherein X is a heterocyclic moiety, W is a specific amidir amidinohydrazone or guanidino moiety, R^1, Y and Z, are set forth in the specification, as well as hydrates, solvates or pharmaceutical acceptable salts thereof, that inhibit a number of proteolytic enzymes are described. Also described are methods for preparing the compoun and using the compounds for inhibiting proteases, for example, thrombin. An exemplary compound has structure (A).

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Amidino and Guanidino Heterocyclic Protease Inhibitors

Background of the Invention

Field of the Invention

The present invention relates to novel compounds that function as enzyme inhibitors, and particularly to a new class of non-peptidic inhibitors of proteolytic enzymes.

Related Art

Proteases are enzymes that cleave proteins at single, specific peptide bonds. Proteases can be classified into four generic classes: serine, thiol or cysteinyl, acid or aspartyl, and metalloproteases (Cuypers *et al.*, *J. Biol. Chem.* *257*:7086 (1982)). Proteases are essential to a variety of biological activities, such as digestion, formation and dissolution of blood clots, reproduction and the immune reaction to foreign cells and organisms. Aberrant proteolysis is associated with a number of disease states in man and other mammals. The human neutrophil proteases, elastase and cathepsin G, have been implicated as contributing to disease states marked by tissue destruction. These disease states include emphysema, rheumatoid arthritis, corneal ulcers and glomerular nephritis. (Barret, in *Enzyme Inhibitors as Drugs*, Sandler, ed., University Park Press, Baltimore, (1980)). Additional proteases such as plasmin, C-1 esterase, C-3 convertase, urokinase, plasminogen activator, acrosin, and kallikreins play key roles in normal biological functions of mammals. In many instances, it is beneficial to disrupt the function of one or more proteolytic enzymes in the course of therapeutically treating a mammal.

Serine proteases include such enzymes as elastase (human leukocyte), cathepsin G, plasmin, C-1 esterase, C-3 convertase, urokinase, plasminogen activator, acrosin, chymotrypsin, trypsin, thrombin, factor Xa and kallikreins.

Human leukocyte elastase is released by polymorphonuclear leukocytes at sites of inflammation and thus is a contributing cause for a number of disease states. Cathepsin G is another human neutrophil serine protease. Compounds with the ability to inhibit the activity of these enzymes are expected to have an anti-inflammatory effect useful in the treatment of gout, rheumatoid arthritis and other inflammatory diseases, and in the treatment of emphysema. Chymotrypsin and trypsin are digestive enzymes. Inhibitors of these enzymes are useful in treating pancreatitis. Inhibitors of urokinase and plasminogen activator are useful in treating excessive cell growth disease states, such as benign prostatic hypertrophy, prostatic carcinoma and psoriasis.

The serine protease thrombin occupies a central role in hemostasis and thrombosis, and as a multifactorial protein, induces a number of effects on platelets, endothelial cells, smooth muscle cells, leukocytes, the heart, and neurons (Tapparelli *et al.*, *Trends in Pharmacological Sciences 14*:366-376 (1993); Lefkovits and Topol, *Circulation 90*(3):1522-1536 (1994); Harker, *Blood Coagulation and Fibrinolysis 5 (Suppl 1)*:S47-S58 (1994)). Activation of the coagulation cascade through either the intrinsic pathway (contact activation) or the extrinsic pathway (activation by exposure of plasma to a non-endothelial surface, damage to vessel walls or tissue factor release) leads to a series of biochemical events that converge on thrombin. Thrombin cleaves fibrinogen ultimately leading to a hemostatic plug (clot formation), potently activates platelets through a unique proteolytic cleavage of the cell surface thrombin receptor (Coughlin, *Seminars in Hematology 31*(4):270-277 (1994)), and autoamplifies its own production through a feedback mechanism. Thus, inhibitors of thrombin function have therapeutic potential in a host of cardiovascular and non-cardiovascular diseases, including: myocardial infarction; unstable angina; stroke; restenosis; deep vein thrombosis; disseminated intravascular coagulation caused by trauma, sepsis or tumor metastasis; hemodialysis; cardiopulmonary bypass surgery; adult respiratory distress syndrome; endotoxic shock; rheumatoid arthritis; ulcerative colitis; induration;

metastasis; hypercoagulability during chemotherapy; Alzheimer's disease; and Down's syndrome.

Factor Xa is another serine protease in the coagulation pathway. Factor Xa associates with factor Va and calcium on a phospholipid membrane thereby forming a prothrombinase complex. This prothrombinase complex then converts prothrombin to thrombin (Claeson, *Blood Coagulation and Fibrinolysis 5*:411-436 (1994); Harker, *Blood Coagulation and Fibrinolysis 5 (Suppl 1)*:S47-S58 (1994)). Inhibitors of factor Xa are thought to offer an advantage over agents that directly inhibit thrombin since direct thrombin inhibitors still permit significant new thrombin generation (Lefkovits and Topol, *Circulation 90*(3):1522-1536 (1994); Harker, *Blood Coagulation and Fibrinolysis 5 (Suppl 1)*:S47-S58 (1994)).

A need continues to exist for non-peptidic compounds that are potent and selective protease inhibitors, and which possess greater bioavailability and fewer side-effects than currently available protease inhibitors. Accordingly, new classes of potent protease inhibitors, characterized by potent inhibitory capacity and low mammalian toxicity, are potentially valuable therapeutic agents for a variety of conditions, including treatment of a number of mammalian proteolytic disease states.

Summary of the Invention

The present invention is directed to novel compounds having Formula *I* (below). Also provided are processes for preparing compounds of Formula *I*. The novel compounds of the present invention are potent inhibitors of proteases, especially trypsin-like serine proteases, such as chymotrypsin, trypsin, thrombin, plasmin and factor Xa. Certain of the compounds exhibit antithrombotic activity via direct, selective inhibition of thrombin, or are intermediates useful for forming compounds having antithrombotic activity. Other compounds are expected to inhibit trypsin and/or chymotrypsin, and are therefore useful in treating pancreatitis. Also provided are methods of inhibiting or treating aberrant

proteolysis in a mammal and methods of treating thrombosis, ischemia, stroke, restenosis or inflammation in a mammal by administering an effective amount of a compound of Formula *I*. Further provided are pharmaceutical compositions comprising a compound of Formula *I* and one or more pharmaceutically acceptable carriers or diluents.

Detailed Description of the Preferred Embodiments

The present invention is broadly directed to compounds sharing a common heteroaryl core and either an amidino or guanidino functionality. The compounds share the ability to inhibit proteases, especially serine proteases, more especially trypsin-like serine proteases. The compounds have the general formula *I*:

$$R^1—Z—X—Y—W \qquad I$$

or solvates, hydrates or pharmaceutically acceptable salts thereof;

wherein:

R^1 is one of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl or heteroaryl, any of which may be optionally substituted;

Z is one of $-NR^{10}SO_2-$, $-SO_2NR^{10}-$, $-NR^{10}C(R^yR^z)-$, $-C(R^yR^z)NR^{10}-$, $-OSO_2-$, $-SO_2O-$, $-OC(R^yR^z)-$, $-C(R^yR^z)O-$, $-NR^{10}CO-$ or $-CONR^{10}-$, where

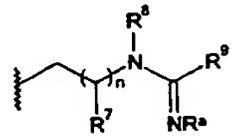
R^y and R^z are each independently one of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, hydroxyalkyl, carboxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl or carboxy, and R^{10} is defined below;

X is a stable 5- to 7-membered monocyclic or 7- to 10-membered bicyclic heterocyclic moiety that is either saturated or unsaturated, and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S, wherein the nitrogen and sulfur heteroatoms can

optionally be oxidized, the nitrogen can optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring, and wherein the heterocyclic ring can be attached to pendant groups Y and Z at any heteroatom or carbon atom that results in a stable formula; and wherein the heterocyclic ring can be optionally substituted on carbon or on a nitrogen atom if the resulting compound is stable;

Y is one of -O-, -NR^{10}-, -S-, -CHR^{10}- or a covalent bond;

W is one of



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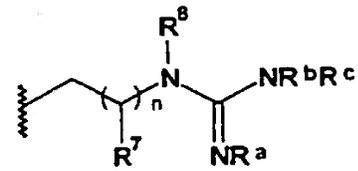

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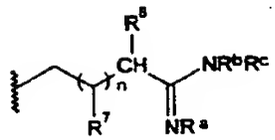

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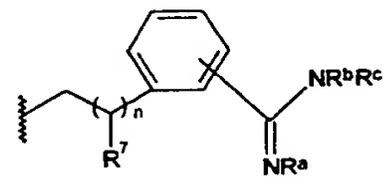

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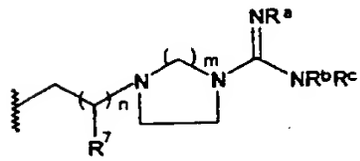

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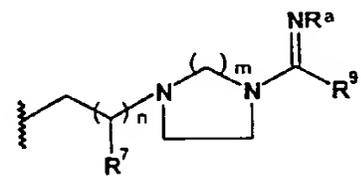

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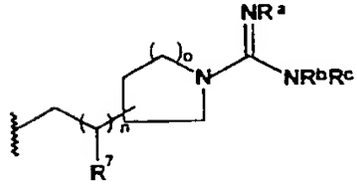

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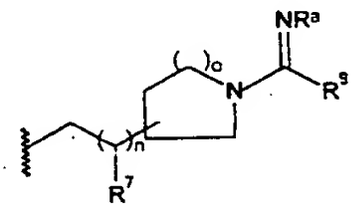

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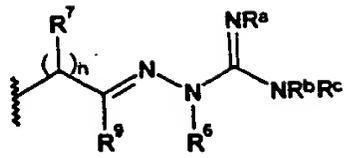


X;

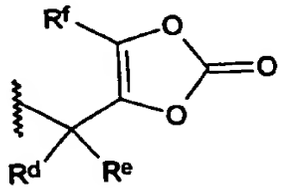
R^6 is one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl, aminoalkyl, monoalkylamino(C_{2-10})alkyl, dialkylamino(C_{2-10})alkyl, carboxyalkyl or $-CO_2R^w$, where R^w is defined below;

R^7 and R^8 are each independently one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl or carboxyalkyl;

R^9 is one of hydrogen, alkyl, cycloalkyl or aryl, wherein said alkyl, cycloalkyl or aryl can be optionally substituted with amino, monoalkylamino, dialkylamino, alkoxy, hydroxy, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, aryl, heteroaryl, acylamino, cyano or trifluoromethyl;

R^{10}, in each instance, is independently one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl, aminoalkyl, monoalkylamino(C_{2-10})alkyl, dialkylamino(C_{2-10})alkyl, alkoxycarbonylalkyl or carboxyalkyl;

R^a, R^b and R^c are each independently one of hydrogen, alkyl, hydroxy, alkoxy, aryloxy, aralkoxy, alkoxycarbonyloxy, cyano or $-CO_2R^w$, where R^w is alkyl, cycloalkyl, phenyl benzyl,



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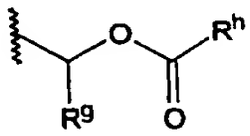


where R^d and R^e are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or phenyl, R^f is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or phenyl, R^g is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or phenyl, and R^h is aralkyl or C_{1-6} alkyl;

n is from zero to 8;

o is from zero to 4; and

m is from 2 to 4.

The term "substituted", as used in reference to the heterocyclic moiety X, means that one or more hydrogens of the moiety are replaced with a selection from the group indicated below, provided that no atom's normal valency is exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens attached to an atom of the moiety are replaced.

By "stable compound" or "stable formula", as recited in the definition of X, is meant herein a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture and formulation into an efficacious therapeutic agent.

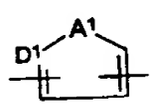
The heterocyclic rings X described herein can be substituted on carbon or on a nitrogen atom if the resulting compound is stable. Examples of useful heterocycles include, but are not limited to, pyridyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, benzothiophenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6*H*-1,2,5-thiadiazinyl, 2*H*,6*H*-1,5,2-dithiazinyl, thiophene(yl), thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathiinyl, 2*H*-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, 1*H*-indazolyl, purinyl, 4*H*-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4a*H*-carbazolyl, carbazolyl, ß-carbolinyl, phenanthridinyl, acridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl or oxazolidinyl.

Preferred heterocycles are aromatic heterocycles, "heteroaryl" groups. The term "heteroaryl" as employed herein refers to heterocyclic groups having 5 to 10 ring atoms; 6 or 10 π electrons shared in a cyclic array; and containing

carbon atoms and 1, 2 or 3 oxygen, nitrogen or sulfur heteroatoms. Examples of heteroaryl groups are: thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, pyranyl, isobenzofuranyl, benzoxazolyl, chromenyl, xanthenyl, phenoxathiinyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinazolinyl, cinnolinyl, pteridinyl, 4a*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl and phenoxazinyl groups.

Additionally, N-oxides of nitrogen containing heteroaryl groups are contemplated. Also, it is understood that additional hydrogen atoms in heterocyclic groups (allowing for attachment to pendant groups Z and Y) can be substituted with C_{1-6} alkyl, C_{3-8} cycloalkyl, phenyl, benzyl, trifluoromethyl, halogen, hydroxy (C_{1-8}) alkyl, cyano, nitro, carboxamido, carboxy, C_{1-4} alkoxycarbonyl, C_{1-4} alkoxymethyl or C_{1-4} alkoxy.

Particularly useful heterocyclic groups have either five or six ring atoms. Useful heteroaryl groups having five ring atoms include:



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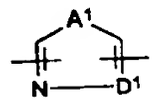

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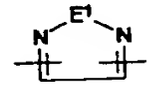

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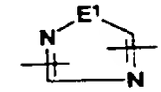
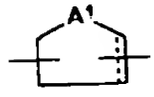


(4)

wherein A^1 is O; S or N(R), wherein R is hydrogen or C_{1-6} alkyl; D^1 is N or CH; and E^1 is O or S.

Useful 5-membered heterocyclic groups that are partially or totally saturated include:



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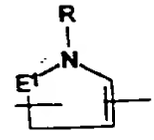

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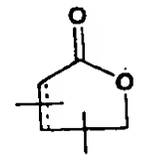

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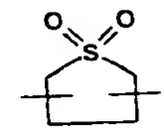

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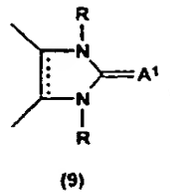

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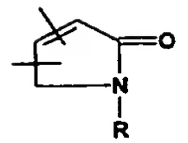

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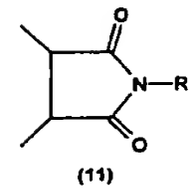
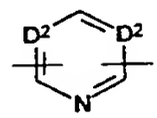


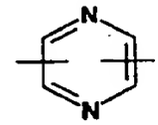
(11)

wherein A^1 and E^1 are defined as above, and wherein R, in each instance, is independently one of hydrogen or C_{1-6} alkyl.

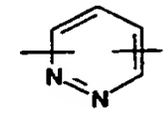
Useful heteroaryl groups having six ring atoms include:



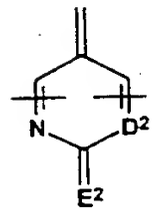
(12)



(13)

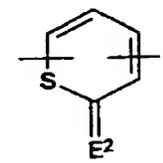


(14)



(15)

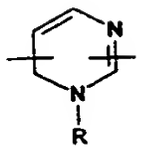
or



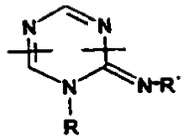
(16)

wherein D^2 is N; $N^+(O^-)$ or CH; and E^2 is O or S.

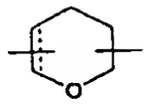
Useful six membered heterocyclic groups that are partially or totally saturated include:



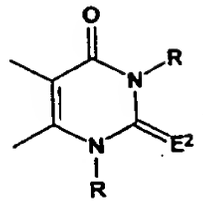
(17)



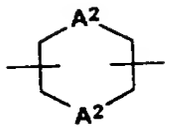
(18)



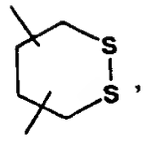
(19)



(20)

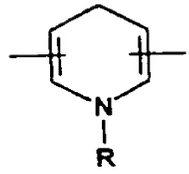


(21)



(22)

or

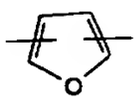


(23)

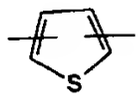
wherein D^2 and E^2 are defined as above; A^2 is independently O, S or N(R), where R is hydrogen or C_{1-6} alkyl; and R' is hydrogen, C_{1-6} alkyl, hydroxy or C_{1-6} alkoxy.

The dashed line, where it appears in the above structures, represents an optional double bond.

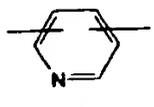
Non-limiting examples of X include:



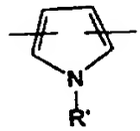
(24)



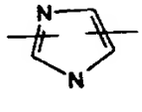
(25)



(26)

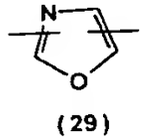


(27)



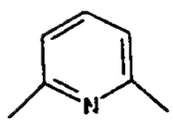
(28)

and

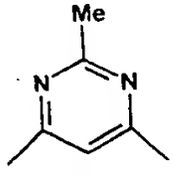


(29)

Preferred values of X include:



(30)



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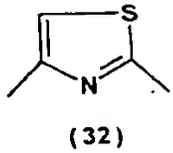
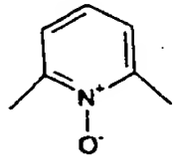
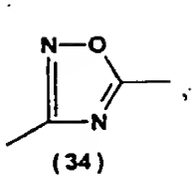


(32)



(33)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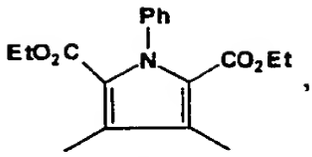
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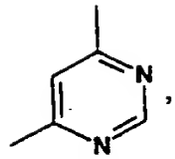
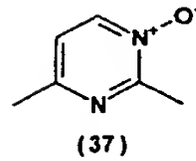
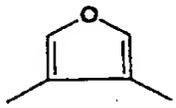

(36)


(37)


(38)

and


(39)

Another preferred set of values include 2,3-pyridyl, 2,4-pyridyl, 2,5-pyridyl, 2,6-pyridyl, 2,4-furanyl, 3,4-furanyl, 2,5-furanyl, 4,5-pyrimidinyl and 4,6-pyrimidinyl.

The groups Y and Z of Formula *I* are each covalently attached to a carbon atom when X is a heteroaryl ring. For example, it is contemplated that when Z is attached to the 2-position of furanyl, thiofuranyl or pyrrolyl, then Y can be attached to the 3, 4, or 5 position of the ring.

Preferred compounds of the present invention are those wherein Y is one of divalent oxygen (—O—) or —NR^{10}— and Z is one of —SO_2NR^{10}—, —SO_2O— or —CH_2O—.

Preferably, R^1 is one of C_{1-12} alkyl, C_{4-7} cycloalkyl, C_{2-8} alkenyl, C_{2-8} alkynyl or C_{6-14} aryl, especially C_{6-10} aryl, any of which is optionally substituted.

Optional substituents on R^1 include one or more, preferably one or two, hydroxy, nitro, trifluoromethyl, halogen, alkoxy, aminoalkoxy, aminoalkyl, hydroxyalkyl, hydroxyalkoxy, cyano, amino, monoalkylamino, dialkylamino, carboxy, carboxyalkyl, carboxyalkoxy, mono(hydroxyalkyl)amino, di(hydroxyalkyl)amino, mono(carboxyalkyl)amino, di(carboxyalkyl)amino, alkoxycarbonylamino, alkoxycarbonyl, aralkoxycarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkylsulfonyl, alkenylsulfonyl, alkynylsulfonyl, alkylsulfinyl, alkylsulfonamido, amidino, guanidino, alkyliminoamino, formyliminoamino, trifluoromethoxy or perfluoroethoxy. A further substituent on aryl, cycloalkyl,

alkenyl, alkynyl and aralkyl moities of R^1 includes one or more, preferably one or two, alkyl moieties.

Preferred values of optional substituents on R^1 include hydroxy, nitro, trifluoromethyl, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{1-6} aminoalkoxy, amino, mono(C_{1-4})alkylamino, di(C_{1-4})alkylamino, C_{2-6} alkoxycarbonylamino, C_{2-6} alkoxycarbonyl, carboxy, C_{1-6} hydroxyalkyl, C_{2-10} mono(carboxyalkyl)amino, di(C_{2-10} carboxyalkyl)amino, C_{6-14} ar(C_{1-6} alkoxycarbonyl, C_{2-6} alkynylcarbonyl, C_{1-6} alkylsulfonyl, C_{2-6} alkenylsulfonyl, C_{2-6} alkynylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonamido, amidino, guanidino, C_{1-6} alkyliminoamino, formyliminoamino, C_{2-6} carboxyalkoxy, carboxyalkylamino, cyano, trifluoromethoxy, and perfluoroethoxy.

An additional preferred group of compounds are those compounds wherein R^1 is heteroaryl or substituted heteroaryl. Preferred R^1 heteroaryl groups include pyridyl, thienyl, chromenyl, benzoxazolyl, quinazolinyl, quinolinyl and tetrahydroquinolinyl, with pyridyl, quinazolinyl, quinolinyl and tetrahydroquinolinyl being most preferred. When R^1 is substituted heteroaryl, those compounds having one of the heteroaryl groups mentioned as preferred, additionally have one or more, preferably one or two, substituents that are listed in the preceding two paragraphs.

Useful values of R^1 include phenyl, chlorophenyl, iodophenyl, dichlorophenyl, bromophenyl, trifluoromethylphenyl, bis(trifluoromethyl)phenyl, methylphenyl, *t*-butylphenyl, aminochlorophenyl, methoxyphenyl, chloromethoxyphenyl, dimethoxyphenyl, hydroxyphenyl, carboxyphenyl, aminophenyl, cyanophenyl, methylaminophenyl, *n*-butylaminophenyl, amidinophenyl, guanidinophenyl, formyliminoaminophenyl, acetimidoylaminophenyl, methoxycarbonylphenyl, ethoxycarbonylphenyl, carboxymethoxyphenyl, naphthyl, hydroxynaphthyl, cyclohexyl, cyclopentyl, 2-propylbutyl, pyridinyl, chloropyridinyl, methylpyridinyl, pyrimidinyl, chloropyrimidinyl, methylpyrimidinyl, quinolinyl and tetrahydroquinolinyl.

Preferably, W is one of Formulae ***III***, ***VI***, ***VII***, ***VIII*** or ***X***.

Preferably, R^6 includes hydrogen, C_{1-6} alkyl, C_{3-8} cycloalkyl, phenyl, benzyl, trifluoromethyl, halogen, hydroxy(C_{1-8})alkyl, cyano, nitro, carboxamide, carboxy, alkoxycarbonyl, alkoxymethyl and alkoxy. Suitable values of R^6 include hydrogen, methyl, methoxy and trifluoromethyl.

Preferably, R^7 and R^8 are independently hydrogen, C_{1-6} alkyl, C_{6-10} ar(C_{1-6})alkyl, C_{6-10} aryl, C_{2-10} hydroxyalkyl or C_{2-7} carboxyalkyl. Useful values of R^7 and R^8 include hydrogen, methyl, ethyl, propyl, *n*-butyl, benzyl, phenylethyl, 2-hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl, 2-carboxymethyl, 3-carboxyethyl and 4-carboxypropyl.

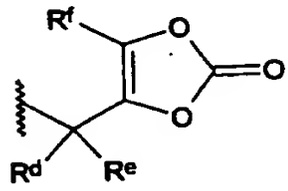
Preferably, R^9 is hydrogen or C_{1-6}alkyl optionally substituted by one, two or three of, preferably one of, amino, monoalkylamino, dialkylamino, alkoxy, hydroxy, alkoxycarbonyl, aryloxycarbonly, aralkoxycarbonyl, carboalkoxy, phenyl, cyano, trifluoromethyl, acetylamino, pyridyl, thienyl, furyl, pyrrolyl or imidazolyl.

Suitable values of R^9 include hydrogen, methyl, ethyl, propyl, *n*-butyl, benzyl, phenethyl, 2-hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl, carboxymethyl and carboxyethyl.

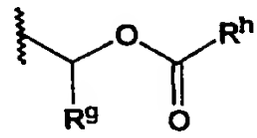
Preferably, R^{10} is hydrogen, C_{1-6} alkyl, C_{6-10} ar(C_{1-6})alkyl, C_{6-10} aryl, C_{2-10} hydroxyalkyl C_{2-10} aminoalkyl, C_{2-7} carboxyalkyl, mono(C_{1-4} alkyl)amino(C_{1-8})alkyl, and di(C_{1-4} alkyl)amino (C_{1-8})alkyl. Suitable values of R^{10} include methyl, ethyl, propyl, *n*-butyl, benzyl, phenylethyl, 2-hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl, 2-aminoethyl, 2-carboxymethyl, 3-carboxyethyl, 4-carboxypropyl and 2-(dimethylamino)ethyl.

Preferred values of R^a, R^b and R^c in Formula ***I*** are hydrogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, cyano or $-CO_2R^w$, where R^w, in each instance, is preferably one of C_{1-4}alkyl, C_{4-7}cycloalkyl or benzyl. Suitable values of R^a, R^b and R^c include hydrogen, methyl, ethyl, propyl, *n*-butyl, hydroxy, methoxy, ethoxy, cyano, $-CO_2CH_3$, $-CO_2CH_2CH_3$ and $-CO_2CH_2CH_2CH_3$. In the most preferred embodiments, R^a, R^b and R^c are each hydrogen.

Also preferred at R^a, R^b and R^c is the group $-CO_2R^w$, where R^w is one of



or



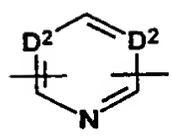
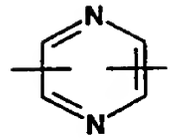
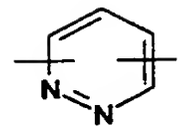
where R^d-R^h are defined as above. When R^a, R^b and R^c are $-CO_2R^w$, where R^w is one of one of these moieties, the resulting compounds are prodrugs that possess desirable formulation and bioavailability characteristics. A preferred value for each of R^d, R^e, and R^g is hydrogen, a preferred value for R^f is methyl, and preferred values for R^h include benzyl and *tert*-butyl.

Preferably, n is from 1 to 6, more preferably from 1 to 4, and most preferably 1 or 2. Preferably, o is from 0 to 3, most preferably 0. 1 or 2. Preferably, m is 2 or 3.

A useful subgenus of compounds falling within the scope of the present invention include compounds of Formula *I* wherein:

R^1 is one of C_{6-10} aryl, pyridinyl, pyrimidinyl, quinizolinyl, quinolinyl or tetrahydroquinolinyl, any of which is optionally substituted by one or two of hydroxy, nitro, trifluoromethyl, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{1-6} aminoalkoxy, amino, mono(C_{1-4})alkylamino, di(C_{1-4})alkylamino, C_{2-6} alkoxycarbonylamino, C_{2-6} alkoxycarbonyl, carboxy, C_{1-6} hydroxyalkyl, C_{2-6} hydroxyalkoxy, C_{2-10} mono(carboxyalkyl)amino, di(C_{2-10} carboxyalkyl)amino, C_{6-14} ar(C_{1-6}) alkoxycarbonyl, C_{2-6} alkynylcarbonyl, C_{1-6} alkylsulfonyl, C_{2-6} alkenylsulfonyl, C_{2-6} alkynylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonamido, amidino, guanidino, C_{1-6} alkyliminoamino, formyliminoamino, C_{2-6} carboxyalkoxy, C_{2-6} carboxyalkyl, carboxyalkylamino, cyano, trifluoromethoxy, and perfluoroethoxy;

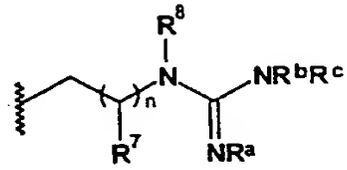
Z is one of $-SO_2O-$, $-SO_2NR^{10}-$, $-C(R^yR^z)O-$ or $-OC(R^yR^z)-$, where R^y and R^z are each hydrogen;

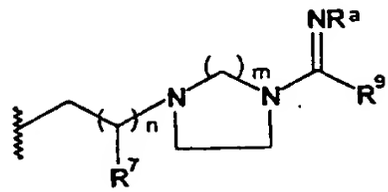
X is one of  ,  , or  ;

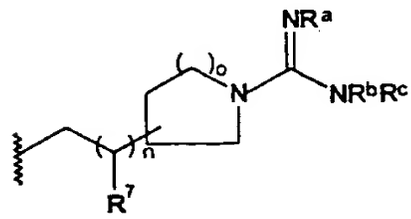
(12) (13) (14)

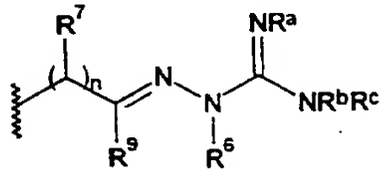
wherein each D^2 is independently N; $N^+(O^-)$ or CH;

W is one of

 *III*

 *VII*

 *VIII* or

 ; *X*

Y is one of –O–, –S–, –NR^{10}–, or a covalent bond;

R^6 is one of hydrogen, C_{1-6} alkyl, C_{6-10} ar(C_{1-6})alkyl, C_{6-10} aryl, C_{2-10} hydroxyalkyl, C_{2-10} aminoalkyl, mono(C_{1-4})alkylamino(C_{2-8})alkyl, di(C_{1-4})alkylamino(C_{2-8})alkyl or C_{2-10} carboxyalkyl;

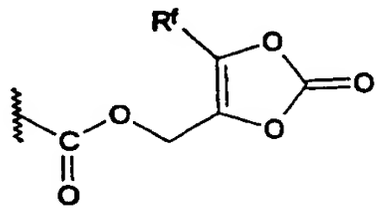
R^7 is one of hydrogen, C_{1-6} alkyl, C_{2-10} carboxyalkyl or C_{2-10} hydroxyalkyl;

R^8 is one of hydrogen, C_{1-6} alkyl, C_{2-10} carboxyalkyl or C_{2-10} hydroxyalkyl;

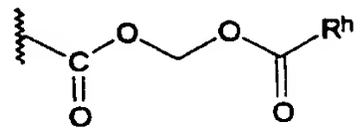
R^9 is hydrogen; or C_{1-10} alkyl, optionally substituted with amino, mono(C_{1-4})alkylamino, C_{1-6} alkoxy, hydroxy, carboxy, phenyl, alkyloxycarbonyl, aralkoxycarbonyl, C_{1-6} acylamino, cyano or trifluoromethyl;

R^{10}, in each instance, is independently hydrogen, C_{1-6} alkyl, benzyl, phenyl, C_{2-10} hydroxyalkyl, C_{2-10} aminoalkyl, C_{1-4} monoalkylamino(C_{2-8})alkyl, C_{1-4} dialkylamino(C_{2-8})alkyl or C_{2-10} carboxyalkyl;

R^a, R^b and R^c are each independently one of hydrogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, phenoxy, C_{1-4} alkyloxycarbonyl, benzyloxycarbonyl, cyano,



or



where R^h is benzyl, methyl, ethyl, isopropyl, *sec*-butyl or *t*-butyl, and where R^f is hydrogen or C_{1-6} alkyl;

n is from zero to 8;

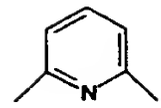
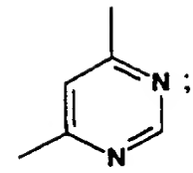
o is from zero to 4; and

m is from 2 to 4.

An especially preferred group of compounds include compounds of Formula *I* wherein:

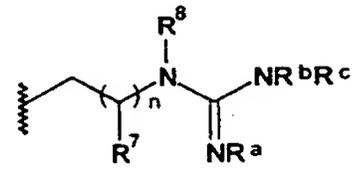
R^1 is one of C_{1-8} alkyl, phenyl or naphthyl, optionally substituted by one or two of chloro, methoxy, trifluoromethyl, amino or dimethylamino;

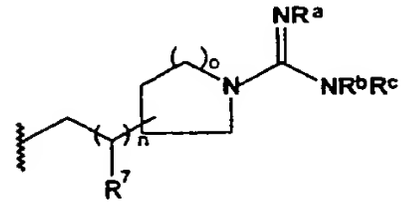
Z is one of –SO_2O–, –SO_2NR^{10}–, –CH_2O– or –OCH_2–;

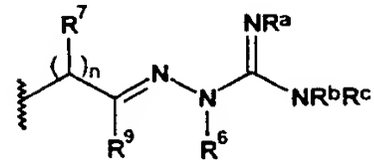
X is one of  or  ;

Y is one of O, NR^{10} or a covalent bond;

W is one of:

 *III* ;

 *VIII* and

 *X*

R^5 is one of hydrogen, C_{1-6} alkyl, C_{2-10} hydroxyalkyl or C_{2-10} carboxyalkyl;

R^6 is hydrogen, C_{1-4} alkyl, C_{2-4} hydroxyalkyl, C_{2-4} carboxyalkyl, C_{2-4} aminoalkyl, dimethylamino(C_{2-8})alkyl, or methylamino(C_{2-8})alkyl;

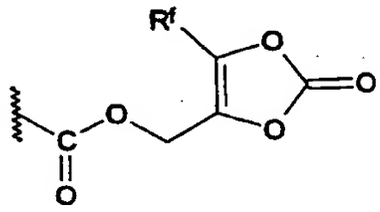
R^7 is one of hydrogen, C_{1-6} alkyl, C_{2-10} hydroxyalkyl or C_{2-10} carboxyalkyl;

R^8 is one of hydrogen, C_{1-6} alkyl, C_{2-10} hydroxyalkyl or C_{2-10} carboxyalkyl;

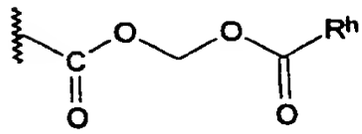
R^9 is one of hydrogen or C_{1-4} alkyl;

R^{10}, in each instance, is independently one of hydrogen, C_{1-4} alkyl, C_{2-4} hydroxyalkyl, C_{2-4} carboxyalkyl, C_{2-4} aminoalkyl, dimethylamino(C_{2-8})alkyl, methylamino(C_{2-8})alkyl;

R^a, R^b and R^c are hydrogen, hydroxy,



or



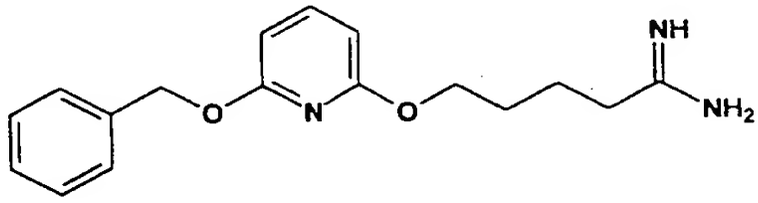
where R^h is benzyl or *t*-butyl, and where R^f is hydrogen or methyl;

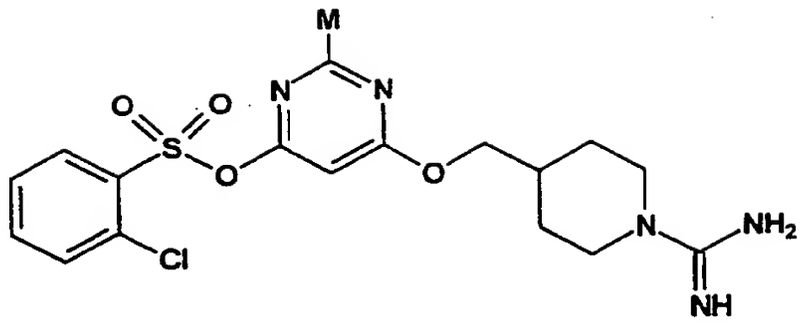
n is from zero to 4;

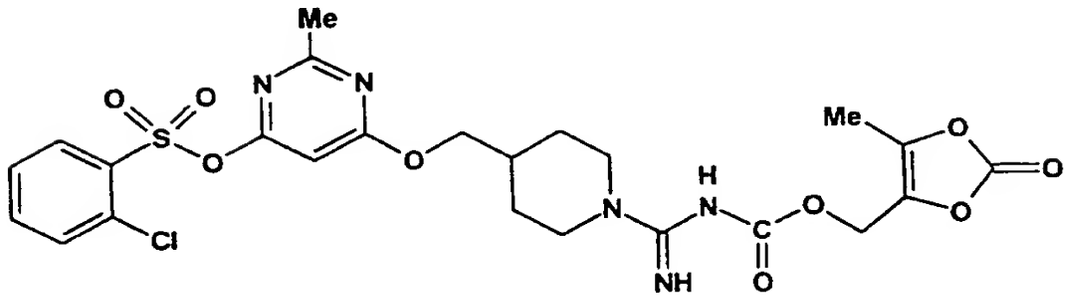
o is 0, 1 or 2; and

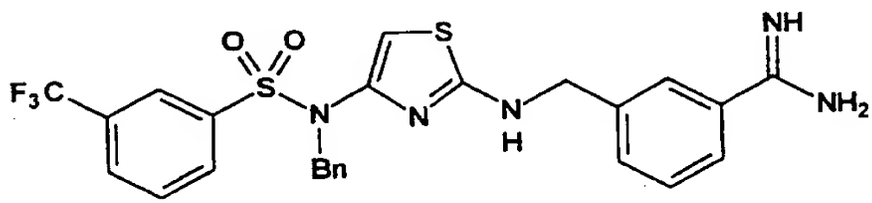
m is 2 or 3.

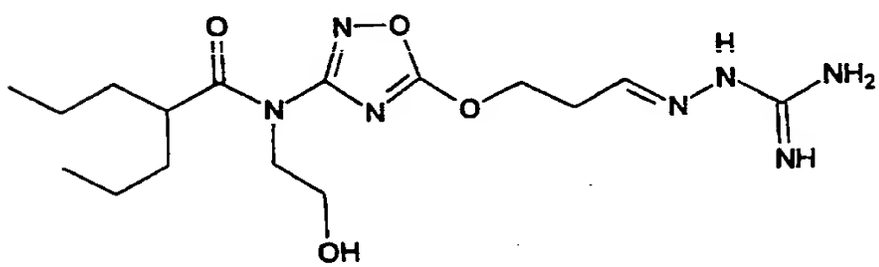
Specific compounds within the scope of the invention include the following examples:

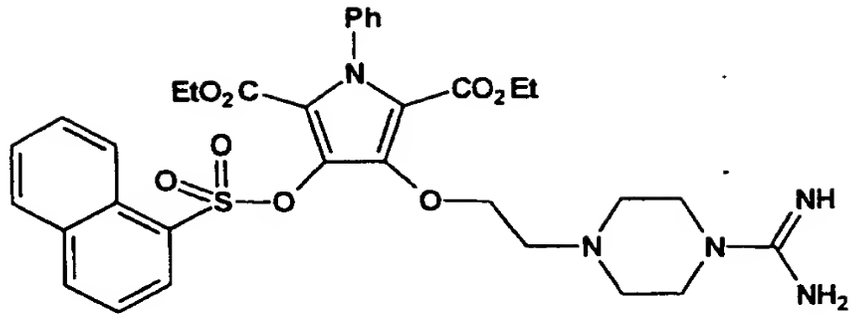






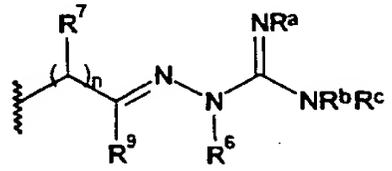






as well as pharmaceutically acceptable salts thereof.

When W is Formula *X*, alternative embodiments of the present invention include compounds of Formula *I* in which two "R" groups together form a saturated or unsaturated hydrocarbon bridge, thus forming an additional cyclic moiety in the resulting compounds. Alternative embodiments include compounds of Formula *I* wherein R^1, Z, X, Y and n are defined as above; W is



X

and:

A. R^7 and R^9 are taken together to form $—(CH_2)_q—$, where q is 1, 2 or 3;
R^6, R^a, R^b and R^c are defined as above; or

B. R^7 is hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl or carboxyalkyl;
R^6 and R^9 are taken together to form $—(CH_2)—(CH_2)—(CH_2)_p—$, where p is 1, 2 or 3; and
R^6, R^a, R^b and R^c are defined as above; or

C. R^6 and R^b are taken together to form =CH—N=CH— or —(CH_2)—$(CH_2)_r$—, where r is 1, 2 or 3;

R^a is hydrogen or hydroxy;

R^c is hydrogen, alkyl, hydroxy, alkoxy, aryloxy, aralkoxy, alkoxycarbamoyloxy, cyano or —CO_2R^w—, where R^w is as defined above;

R^7 is one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl or carboxyalkyl; and

R^9 is one of hydrogen, alkyl, cycloalkyl or aryl, wherein said alkyl, cycloalkyl or aryl can be optionally substituted with amino, monoalkylamino, dialkylamino, alkoxy, hydroxy, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, aryl, heteroaryl, acylamino, cyano or trifluoromethyl; or

D. R^a and R^c are taken together to form —CH_2—$(CH_2)_s$—, where s is 1 or 2;

R^6 is hydrogen, alkyl, alkoxy, aryloxy, aralkoxy, alkoxycarbonyloxy, cyano or —CO_2R^w—, where R^w is as defined above;

R^7 is one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl or carboxyalkyl; and

R^9 is one of hydrogen, alkyl, cycloalkyl or aryl, wherein said alkyl, cycloalkyl or aryl can be optionally substituted with amino, monoalkylamino, dialkylamino, alkoxy, hydroxy, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, aryl, heteroaryl, acylamino, cyano or trifluoromethyl.

It is also to be understood that the present invention is considered to include stereoisomers as well as optical isomers, e.g. mixtures of enantiomers as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in selected compounds of the present series.

The compounds of Formula *I* may also be solvated, especially hydrated. Hydration may occur during manufacturing of the compounds or compositions comprising the compounds, or the hydration may occur over time due to the hygroscopic nature of the compounds.

The term "aryl" as employed herein by itself or as part of another group refers to monocyclic or bicyclic aromatic groups containing from 6 to 12 carbons in the ring portion, preferably 6-10 carbons in the ring portion, such as phenyl, naphthyl or tetrahydronaphthyl.

The term "heteroaryl" as employed herein for all groups other than "X" in Formula I refers to groups having 5 to 14 ring atoms; 6, 10 or 14 π electrons shared in a cyclic array; and containing carbon atoms and 1, 2 or 3 oxygen, nitrogen or sulfur heteroatoms (where examples of heteroaryl groups are: thienyl, benzo[b]thienyl, naphtho[2,3-b]thienyl, thianthrenyl, furyl, pyranyl, isobenzofuranyl, benzoxazolyl, chromenyl, xanthenyl, phenoxathiinyl, 2*H*-pyrrolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, 3*H*-indolyl, indolyl, indazolyl, purinyl, 4*H*-quinolizinyl, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinazolinyl, cinnolinyl, pteridinyl, 4a*H*-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenazinyl, isothiazolyl, phenothiazinyl, isoxazolyl, furazanyl and phenoxazinyl groups).

The term "aralkyl" or "arylalkyl" as employed herein by itself or as part of another group refers to C_{1-6} alkyl groups having an aryl substituent, such as benzyl, phenylethyl or 2-naphthylmethyl.

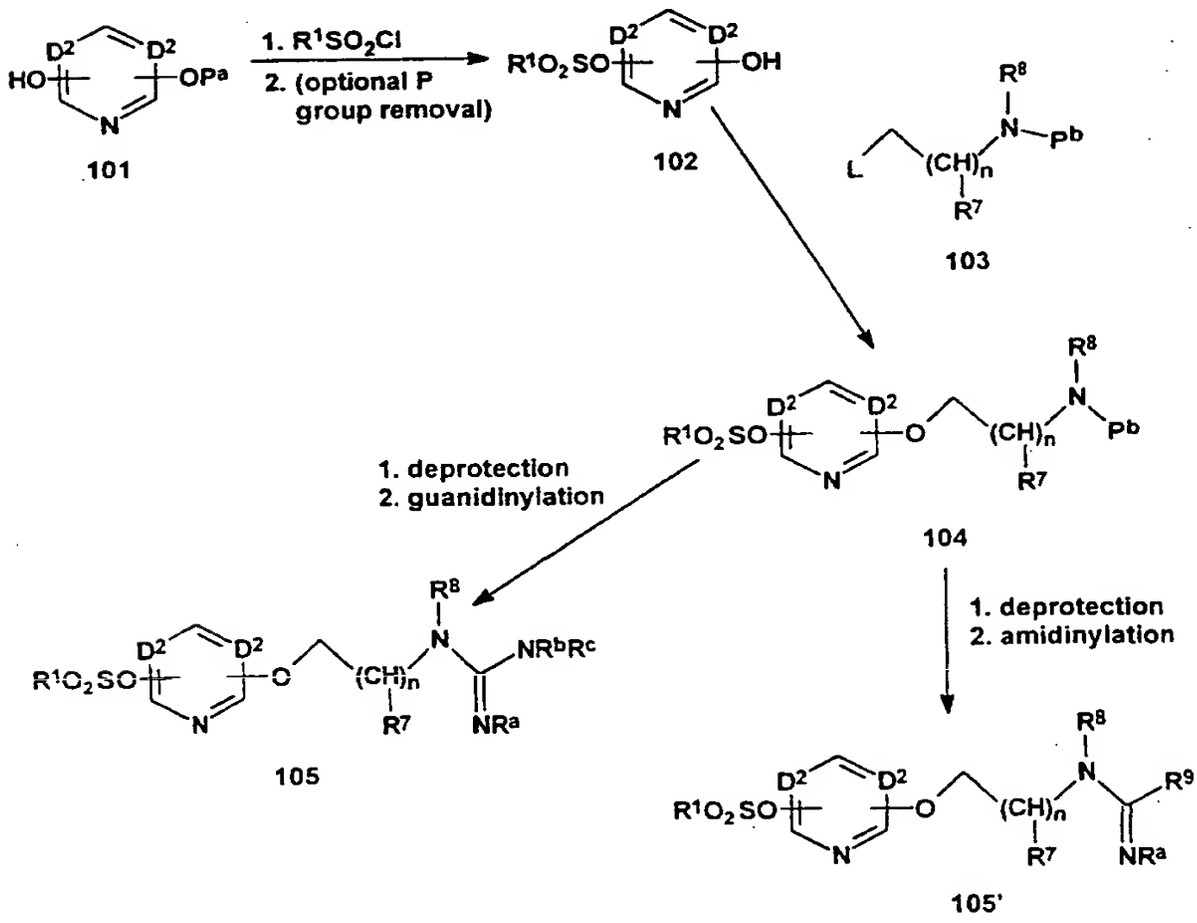
The term "cycloalkyl" as employed herein by itself or as part of another group refers to cycloalkyl groups containing 3 to 9 carbon atoms. Typical examples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl and cyclononyl.

The term "halogen" or "halo"as employed herein by itself or as part of another group refers to chlorine, bromine, fluorine or iodine with chlorine being preferred.

The following schemes exemplify the synthesis of compounds of the present invention. A narrowly defined group of 6-ring membered heteraryl moieties are employed as exemplary starting materials. It will be understood that the following methods are broadly applicable to the full scope of the present invention by substituting the appropriate heterocyclic starting material for the starting materials disclosed in the schemes.

Scheme *Ia* illustrates the preparation of compounds of Formula *I* where $-Z-R^1$ is $-OSO_2-R^1$, Y is divalent oxygen (—O—), X is a nitrogen containing 6-member heteroaryl group and W is a guanidino moiety of Formula *III* or an amidino moiety of Formula *II*.

Scheme Ia



R^1, D^2, R^7, R^8, R^9, R^a, R^b, R^c and n are as defined above for Formula *I*; P^a is a hydroxyl protecting group or hydrogen, and P^b is an amino protecting group.

Heteroaryl diols, such as the 6-membered heteroaryl group **101** (where P^a is H), are converted to monosulfonates **102** by treatment with appropriate sulfonyl chlorides. Examples of **101** include 4,6-dihydroxy-2-methylpyrimidine and 2,4-dihydroxypyridine (available from Aldrich Chemical Co. Milwaukee, WI). Similarly, other available heteroaryl diols can be employed, such as 2,4-dihydroxy-3-phenylisoxazole (available from Lancaster Synthesis Inc., Windham, NH). Preferred conditions include treating heteroaryl diol **101** with a sulfonyl chloride in a biphasic system composed of ether and an aqueous phase saturated with $NaHCO_3$. Alternatively, the reaction may be effected first by deprotonating **101** with a strong base, most preferably NaH, in a polar organic solvent, such as DMF or tetrahydrofuran, followed by treating the deprotonated alcohol with the sulfonyl chloride. Still alternatively, diol **101**, in a typical organic solvent, such as methylene chloride, may be converted to **102** by treating the diol with sulfonyl chloride in the presence of an amine base, such as N-methylmorpholine.

Heteroaryl diols **101** may be monoprotected (P^a is a protecting group) with a variety of protecting groups known in the art, such as esters and benzyl ethers (Green, T.W. & Wuts, P.G.M., *Protective Groups in Organic Synthesis*, 2nd edition, John Wiley and Sons, Inc., New York (1991)). Deprotection of the hydroxyl groups is routinely accomplished using reaction conditions well-known in the art. For example, deprotection of benzyl ethers may be effected through catalytic hydrogenation using palladium on carbon as a catalyst in solvents such as ethanol or tetrahydrofuran. Deprotection of an acetate is accomplished by basic hydrolysis, most preferably with sodium hydroxide in aqueous tetrahydrofuran.

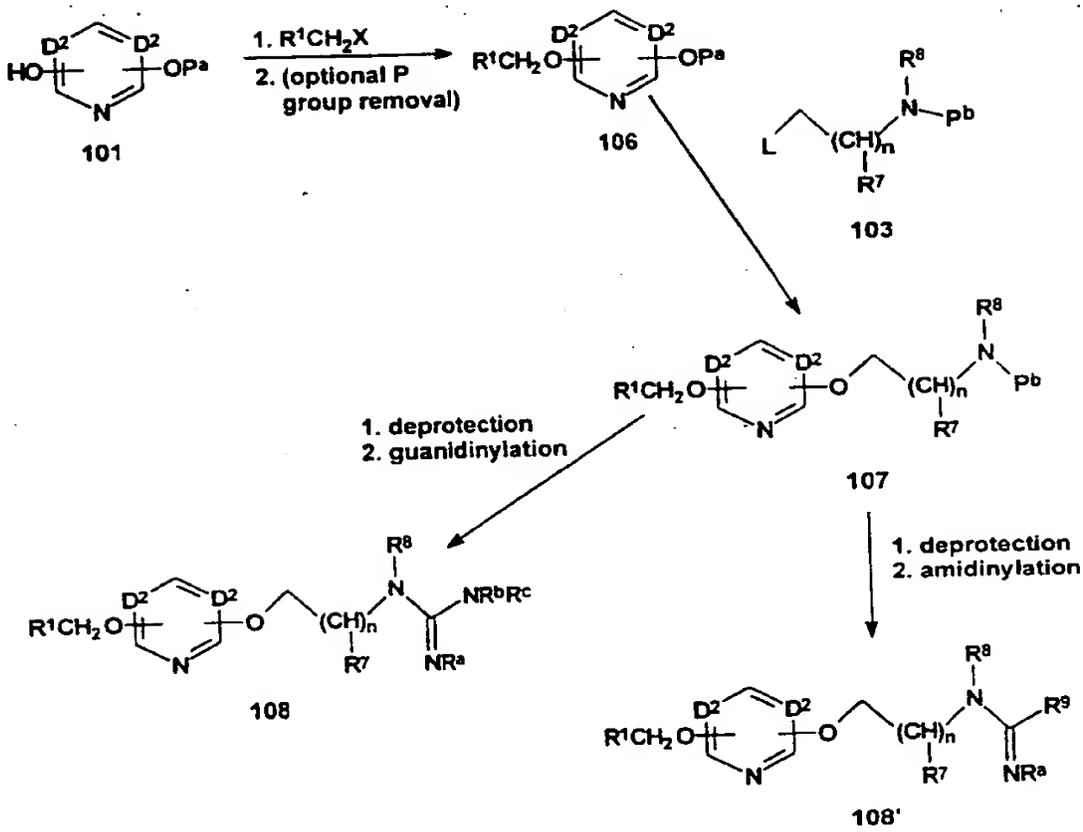
Monosulfonylated heteroaryl diols **102** are coupled to **103** (for L = OH) using a Mitsunobu coupling procedure (Mitsunobu, O., *Synthesis* 1 (1981)) to provide intermediate **104**. Preferred coupling conditions include using a trialkylphosphine or triarylphosphine, such as triphenylphosphine, in a suitable

solvent, such as tetrahydrofuran or methylene chloride, and a dialkyl azodicarboxylate, such as diethyl azodicarboxylate, or an (azodicarbonyl)diamine, such as 1,1'-(azodicarbonyl)dipiperidine (Tsunoda *et al., Tetrahedron Letters 34*:1639 (1993)). In some cases, it is advantageous to add an amine base such as N-methylmorpholine. The amine terminus of **103** is protected with a protecting group P^b that is readily removed from **104**. Amino-protecting groups are well known in the art (Greene, T.W. & Wuts, P.G.M., *Protective Groups in Organic Synthesis*, 2nd edition, John Wiley and Sons, Inc., New York (1991)). Deprotection of the amino group is effected by employing reaction conditions that are well known in the art. For example, the *t*-butoxycarbonyl (BOC) may be removed by exposure to strongly acidic medium, such as hydrogen chloride, in a suitable solvent, such as dioxane, or a mixed trifluoroacetic acid/methylene chloride solvent system. Benzyloxycarbonyl (CBZ) groups may be removed by hydrogen using palladium on carbon as a catalyst in solvents such as ethanol or tetrahydrofuran.

The resulting amine is then converted to guanidine **105** using standard reagents such as aminoiminomethanesulfonic acid (Miller, A.E. & Bischoff, J.J., *Synthesis*, 777 (1986)) or 1*H*-pyrazole-1-carboxamidine hydrochloride (Bernatowicz, M.S. *et al., J. Org. Chem. 57*(8):2497 (1992)). Alternatively, the resulting amine is then converted to amidine **105'** in a manner similar to the procedure described by Nagahara *et al., J. Med. Chem. 37*(8):1200-1207 (1994) wherein the amine is treated with an appropriate imidate in the presence of a base, such as N,N-diisopropylethylamine, in an appropriate solvent, such as DMF. Alternatively, the amine is treated with an appropriate imidate in the presence of a base, such as sodium hydroxide, in an appropriate solvent, such as methanol.

Scheme ***Ib*** illustrates the preparation of compounds of the present invention where $-Z-R^1$ is $-OCH_2-R^1$, Y is divalent oxygen, and W is a guanidino moiety of Formula ***III*** or an amidino moiety of Formula ***II***.

Scheme Ib



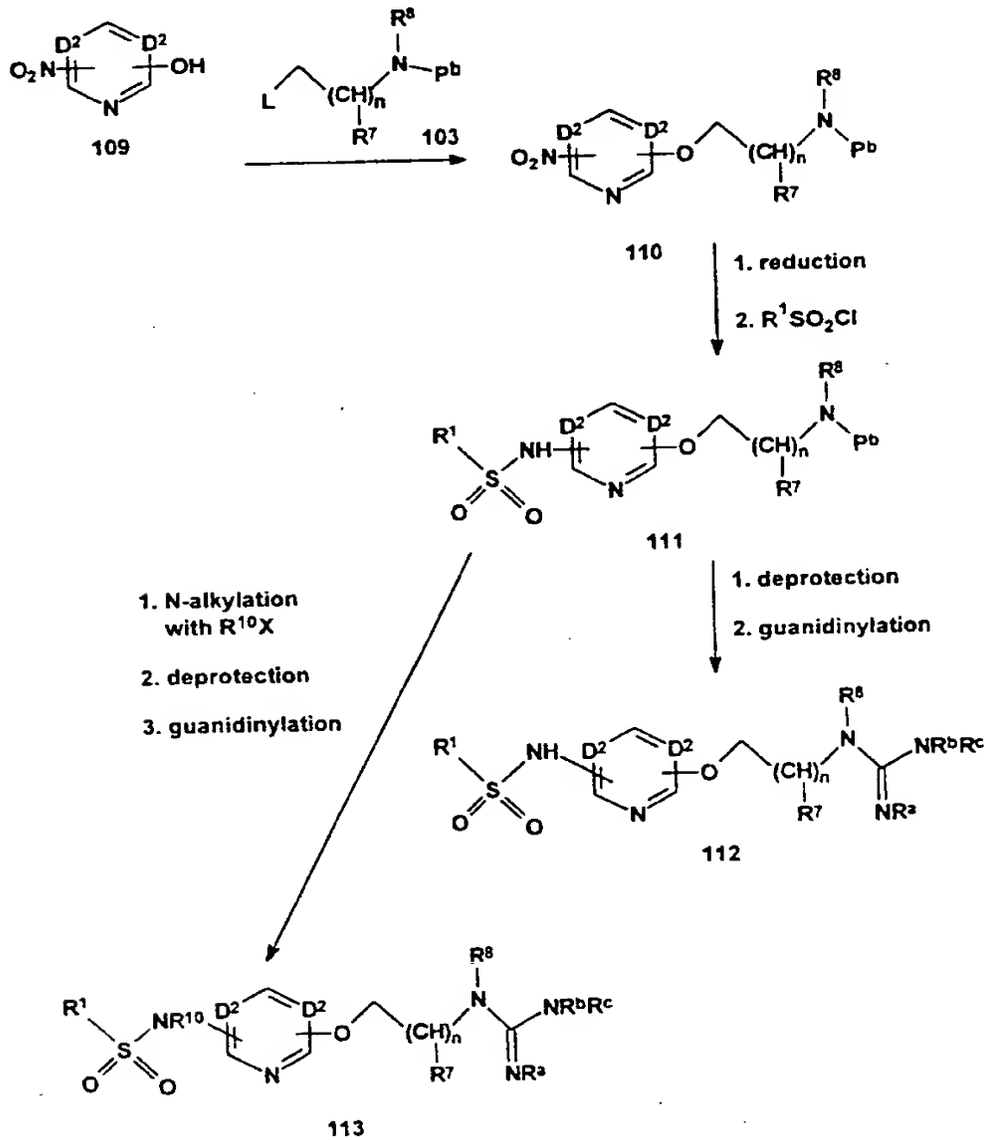
R^1 D^2, R^7, R^8, R^9, R^a, R^b, R^c, n, P^a and P^b are each as defined above.

Heteroaryl ethers **108** are synthesized in a fashion analogous to synthesis of **105**. Heteroaryl diol **101** (P is H) is converted to aryl ether derivative **106** by treating **101** with a strong base, preferably NaH, in a suitable solvent such as DMF, followed by addition of a reactive alkyl or benzyl compound $R'CH_2X$ (where X is a reactive functional group, such as iodide, chloride, bromide or alkylsulfonate). Alternatively, the Mitsunobu reaction may be used with an appropriate R^1CH_2X (X = OH) using the reaction conditions described above. The use of suitable alcohol protecting groups (P^a), such as esters, to suppress over-alkylation, is well known in the art (Greene, T.W. & Wuts, P.G.M., *Protective Groups in Organic Synthesis*, 2nd edition, John Wiley and Sons, Inc., New York (1991)). The protecting group may then be removed using well-known

techniques, for example by hydrolysis with aqueous NaOH, when an ester protecting group is employed. Heteroaryl ether alcohol **106** is then converted to guanidine **108** using the conditions described for formation of **105**, and converted to amidino compound **108'** using conditions described for the formation of **105'**.

Scheme ***IIa*** depicts synthetic routes to additional compounds of Formula ***I*** where $-Z-R^1$ is $-NR^{10}SO_2-R^1$, Y is divalent oxygen and W is a guanidino moiety of Formula ***III*** or an amidino moiety of Formula ***II***.

Scheme IIa



R^1, D^2, R^7, R^8, R^{10}, R^a, R^b, R^c, n, P^a and P^b are as defined above.

According to Scheme ***IIa***, a nitroheteroaryl alcohol **109** may be coupled to compound **103** by standard techniques. An example of a useful nitroheteroaryl alcohol is 2-hydroxy-3-nitropyridine (available from Aldrich). Preferably, the reaction is effected by the Mitsunobu reaction (where L is OH). Alternatively, **109** may be treated with a base, such as NaH, in a suitable solvent such as DMF or THF, followed by addition of **103** (where L is a reactive group, such as Cl, Br, I or alkylsulfonate). The nitro group is thereafter reduced, for example, by catalytic reduction using palladium on carbon in a suitable solvent such as ethanol or tetrahydrofuran. The resulting product is then treated with an appropriate sulfonyl chloride (R^1SO_2Cl) to provide **111**.

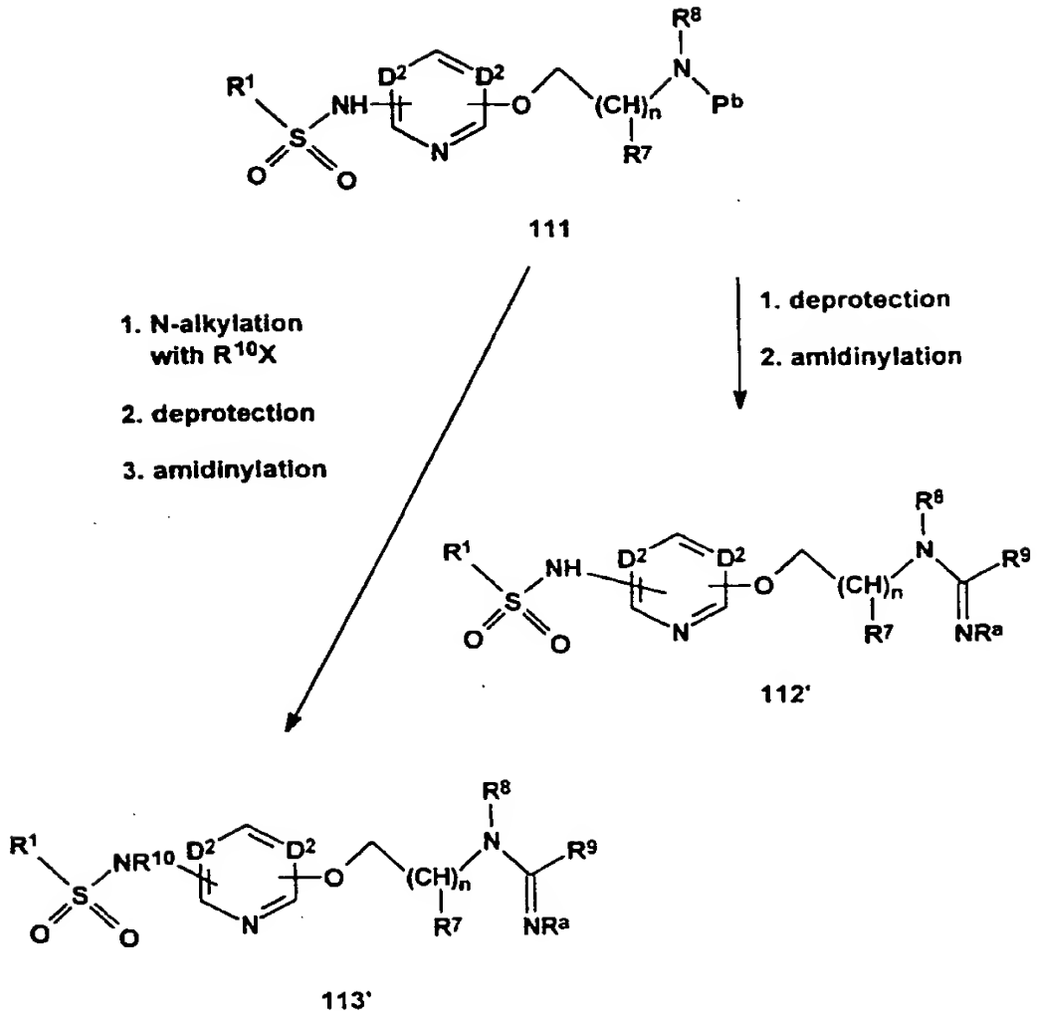
Alternatively, **111** can be synthesized from an aminoheteroaryl alcohol by selective sulfonylation with an appropriate sulfonyl chloride (R^1SO_2Cl) in the presence of a weak base, such as pyridine, followed by coupling with **103**. Useful aminoheteroaryl alcohol starting materials include 3-amino-5-hydroxypyrazole and 2-amino-3-hydroxypyridine (both available from Aldrich).

Removal of the amine protecting group P^b of **111** may be accomplished by techniques known in the art. For example, the *t*-butoxycarbonyl (BOC) is removed by exposure to a strongly acidic medium, such as hydrogen chloride in a suitable solvent, such as dioxane or trifluoroacetic acid in methylene chloride. Benzyloxycarbonyl (CBZ) groups are removed by catalytic hydrogen using palladium on carbon as a catalyst in solvents, such as ethanol or tetrahydrofuran. The deprotected amine is converted to guanidine **112** using standard reagents, such as aminoiminomethanesulfonic acid (Miller, A.E. & Bischoff, J.J., *Synthesis*, 777(1986)) or 1*H*-pyrazole-1-carboxamidine hydrochloride (Bernatowicz, M.S. *et al.*, *J. Org. Chem.* *57*(8):2497 (1992)). Alternatively, bis-(*tert*-butoxycarbonyl)/guanylpyrazole (Bernatowicz, M.S. *et al.*, *Tetrahedron Lett.* *34*(2):3389 (1993)) may be used, which, after deprotection with an acidic medium, such as HCl or trifluoroacetic acid, provides **112**.

N-Substituted sulfonamide derivative **113** is obtained by alkylation of **111** employing a suitable alkylating agent ($R^{10}X$) in the presence of a base, most preferably Cs_2CO_3 used in a polar solvent such as DMF. Deprotection and guanidinylation are then executed in a manner similar to the conversion of **111** to **112**.

The amine **111** can also be converted to amidine **112'** in a manner similar to the procedure described by Nagahara *et. al., J. Med. Chem. 37*(8):1200-1207 (1994) as illustrated below in Scheme ***IIb***. Amine **111** is treated with an appropriate imidate in the presence of a base such as N,N-diisopropylethylamine in an appropriate solvent such as DMF. Alternatively, the amine is treated with an appropriate imidate in the presence of a base such as sodium hydroxide as base in an appropriate solvent such as methanol. N-Substituted sulfonamide dervative **113'** is obtained by alkylation of **111** employing a suitable alkylating agent ($R^{10}X$) in the presence of a base, most preferably Cs_2CO_3 using a polar solvent such as DMF. Deprotection and amidinylation to form **113'** are then executed in a manner similar to the conversion of **111** to **113**.

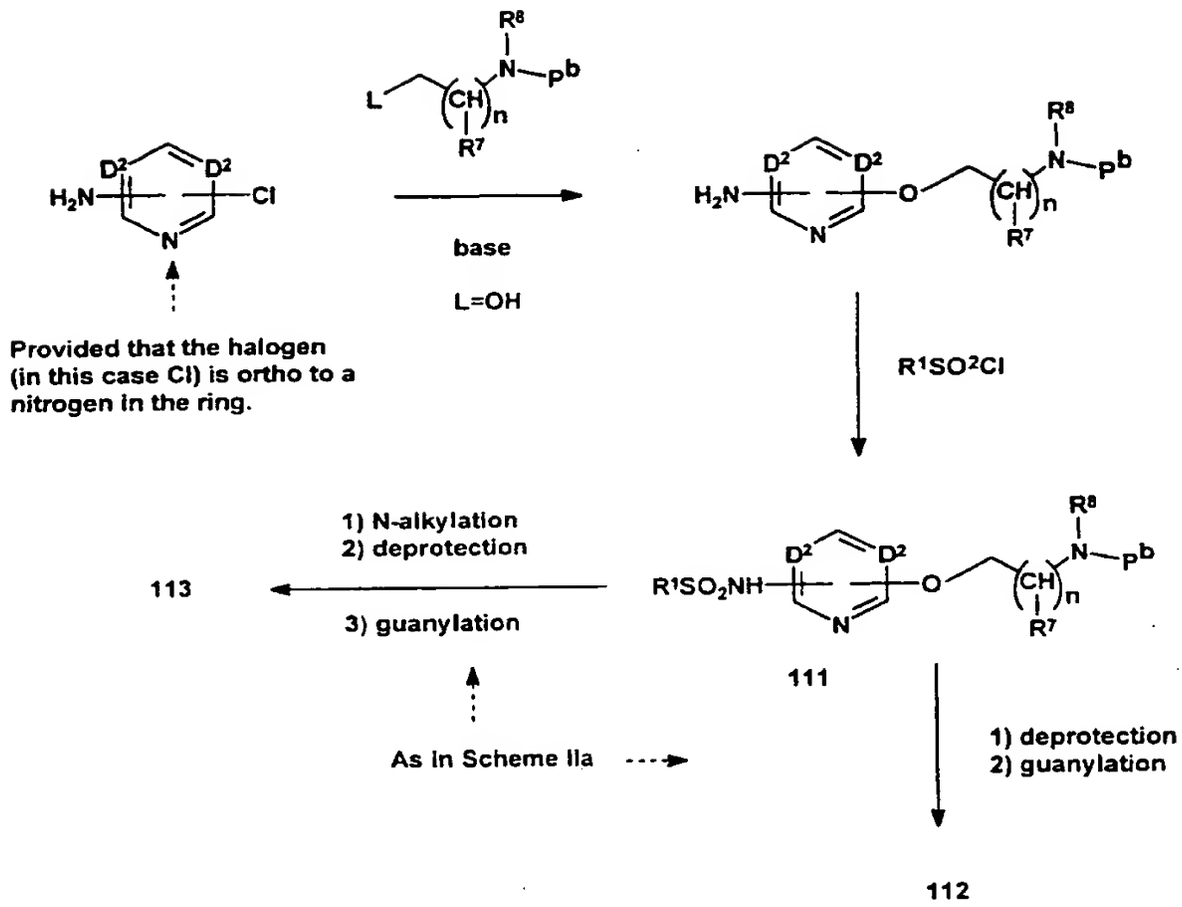
Scheme IIb



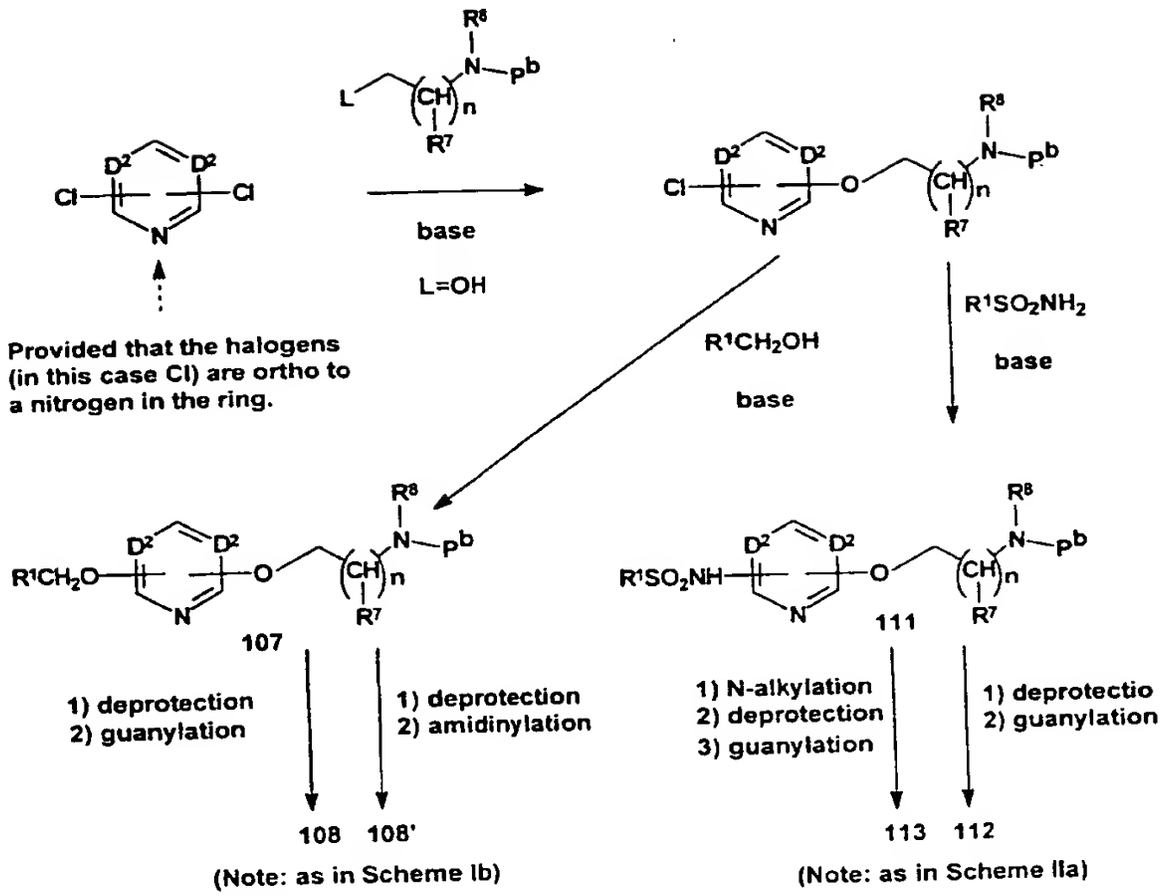
R^1, D^2, R^7, R^8, R^9, R^{10}, R^a, R^b, R^c, n, P^a and P^b are as defined above.

Alternative routes for forming compounds within the scope of Formula *I* are described in Schemes *IIc* and *IId*. Reaction conditions for individual steps are generally the same as described elsewhere in the application.

Scheme IIc

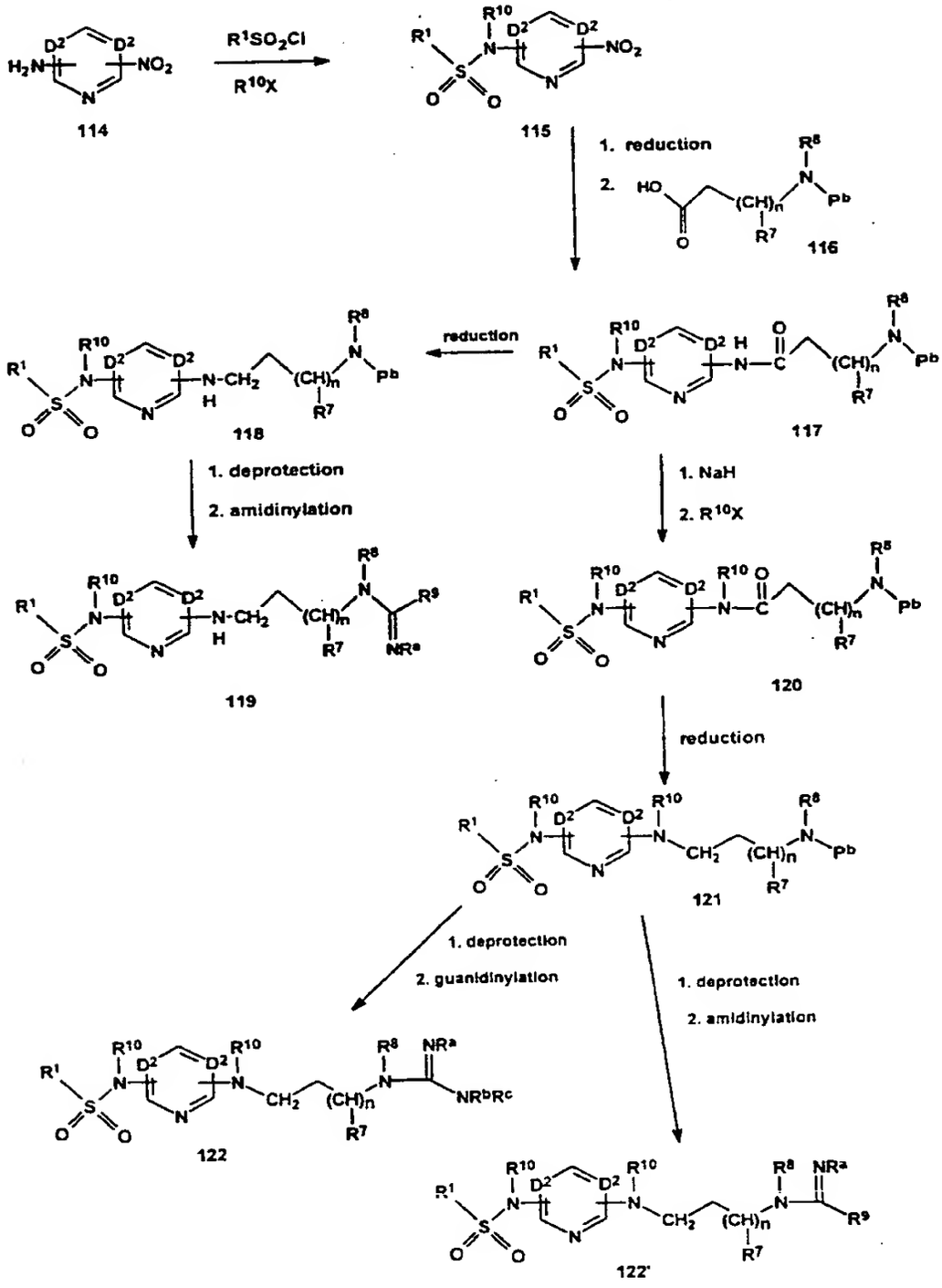

Provided that the halogen (in this case Cl) is ortho to a nitrogen in the ring.
base
L=OH
R¹SO²Cl
1) N-alkylation
2) deprotection
3) guanylation
113
111
As in Scheme IIa
1) deprotection
2) guanylation
112

Scheme IId



Additional compounds within the scope of Formula *I* may be prepared by Scheme *III*.

Scheme III



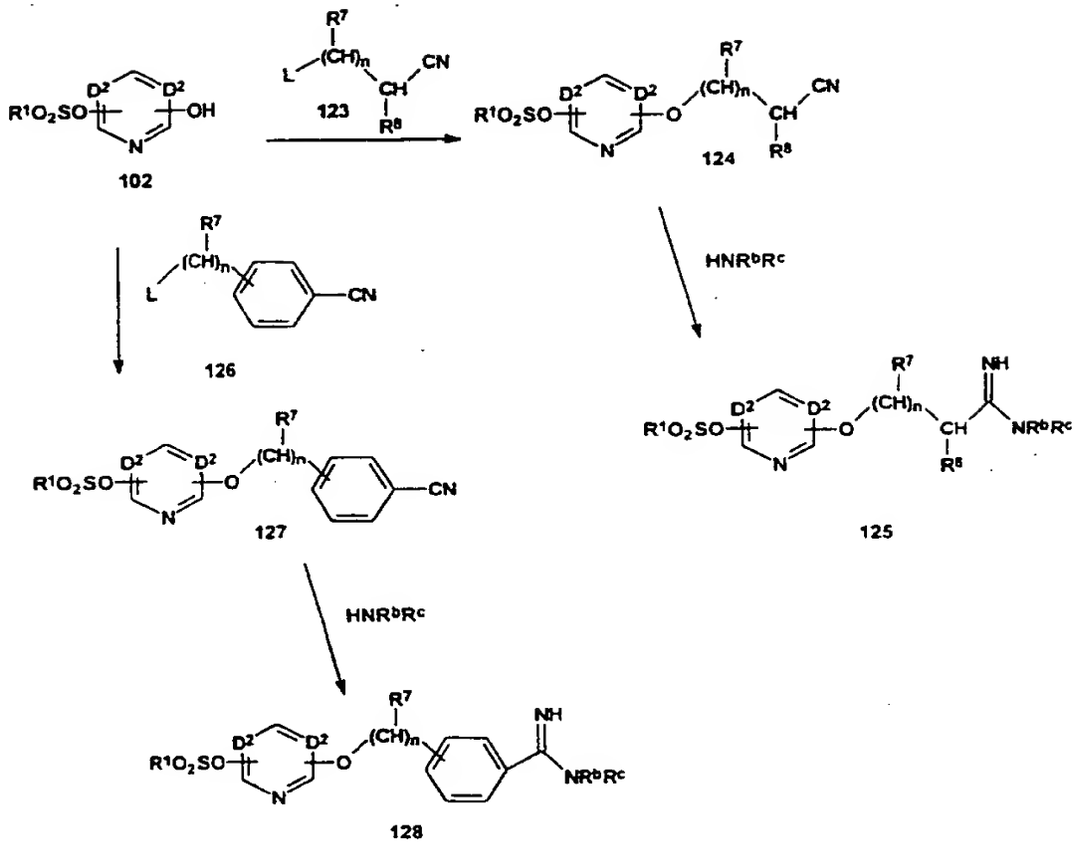
114 115 116 117 118 119 120 121 122 122'

R^1, D^2, R^7, R^8, R^9, R^{10}, R^a, R^b, R^c, n, and P^b are each as defined above.

According to Scheme *III*, a nitroheteroarylamine **114** is converted to a sulfonamide by treatment with an appropriate sulfonyl chloride R^1SO_2Cl in the presence of a weak base, such as N-methylmorpholine. Examples of useful nitroheteroaryl amine starting materials include 2-amino-5-nitrothiazole and 3-amino-4-nitrofurozan (both available from Aldrich). The resulting sulfonamide nitrogen is alkylated with a suitable alkylating agent ($R^{10}X$) in the presence of a base, preferably an alkali metal carbonate such as Cs_2CO_3 or K_2CO_3, using a polar solvent, such as DMF, to provide intermediate **115**. After reduction of the nitro group, the resulting amine is coupled to a carboxylic acid, **116**, to provide amide **117**. Amide coupling may be performed using any of a number of common peptide coupling reagents. Preferably, one of 1,3-dicyclohexylcarbodiimide or Castro's reagent (BOP) are employed (B. Castro *et al.*, *Tetrahedron Lett.*:1219 (1975)). Alternatively, **117** may be formed by coupling the sulfonamidoheteroarylamine with the corresponding acid chloride of acid **116** in the presence of an acid scavenger, such as N-methylmorpholine. Amide **117** is converted to amine **118** by reduction of the amide functionality with an appropriate hydride reagent, preferably borane-THF complex or chlorotrimethylsilane and lithium borohydride. This reaction occurs in a suitable polar solvent, such as THF. Removal of the amine protecting group P^b and formation of the guanidine, as described in Scheme *II*, provides the desired compound **119**. The amide nitrogen may be alkylated using a strong base, such as sodium hydride, in a suitable polar solvent such as DMF, followed by treatment with an alkylating agent ($R^{10}X$) to afford intermediate **120**. Reduction of the amide, as executed in the formation of **118**, to give **121** followed by deprotection and guanidinylation as previously described provides the analogous compound **122** or amidinylation to provide **122'**.

Scheme *IV* illustrates the preparation of compounds of Formula *I* wherein W is an amidino moiety of Formula *IV* or a benzamidino moiety of Formula *V*.

Scheme IV



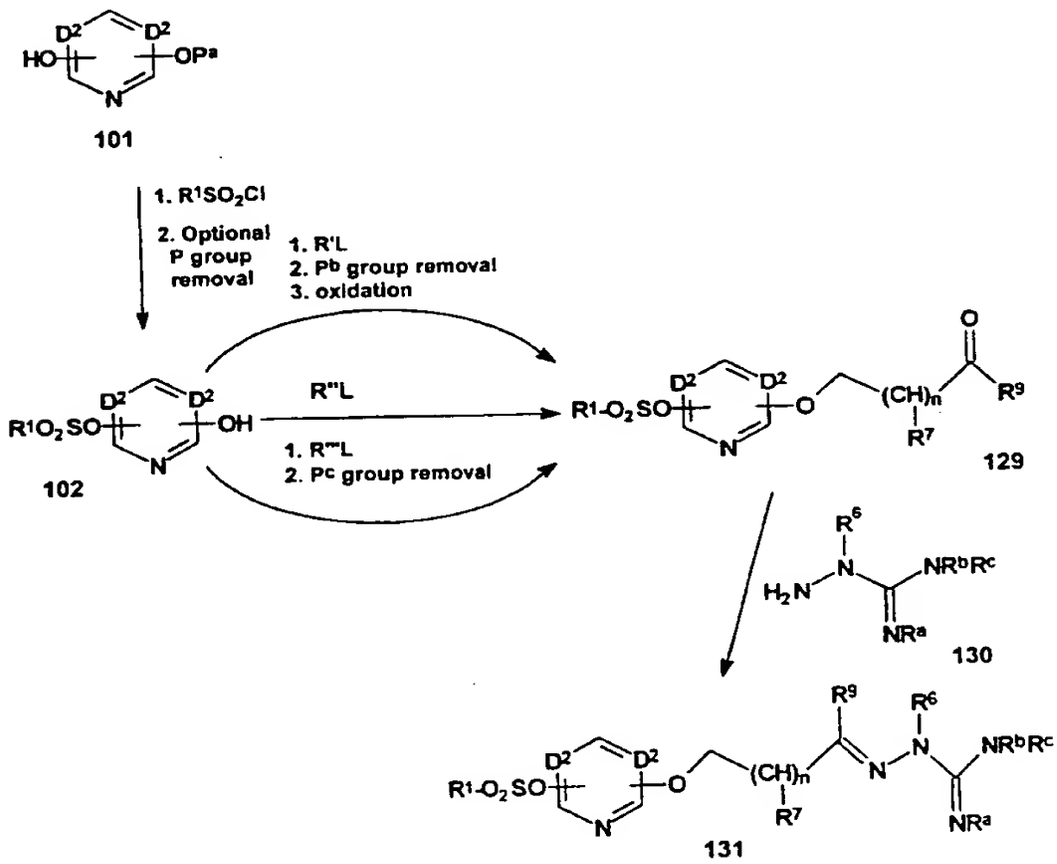
R^1, D^2, R^b, R^c, R^7, R^8 and n are each as defined above.

Monosulfonylated heteroaryl diols **102** are converted to cyano derivatives **124** by exposing **102** to a base, most preferably sodium hydride in a suitable solvent such as DMF, followed by addition of **123**, where L is a reactive group such as iodide, chloride, bromide, alkyl sulfonate, or aryl sulfonate. Alternatively, the Mitsunobu reaction may be used with an appropriate alcohol **123**, where L = OH. The nitrile is submitted to amidine formation conditions such as those described by Nagahara *et. al.*, *J. Med. Chem. 37*(8):1200-1207 (1994), wherein the nitrile is first exposed to a strong acid, preferably hydrogen chloride, in a suitable alcoholic solvent, preferably methanol or ethanol, which converts the nitrile to an imidate. Following brief isolation, the imidate is treated with an appropriate amine HNR^bR^c to effect formation of **125**. Similarly,

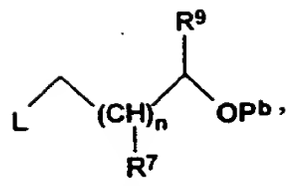
heteroarylamidines **128** are prepared from **102** using appropriate heteroarylnitrile derivatives **126**.

Scheme *V* illustrates the preparation of amidinohydrazone compounds of the present invention wherein W is Formula *X*.

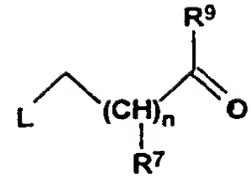
Scheme V



where

R'L is 

132

R''L is 

133

R'''L is the same as **133**, except that the keto or aldehyde group is protected with a suitable protecting group, P^c, and the remaining groups are as defined above.

Diols **101** (where P is H) are converted to monosulfonylated diols **102** by treatment with appropriate sulfonyl chlorides as discussed above in Scheme *I*.

Monosulfonylated diols **102** are coupled to **132** (for L = OH) using a Mitsunobu coupling procedure (Mitsunobu, O., *Synthesis* 1 (1981)), where P^b of **132** may be a suitable alcohol protecting group. Preferred coupling conditions include using a trialkylphosphine or triarylphosphine, such as triphenylphosphine, in a suitable solvent such as tetrahydrofuran or methylene chloride, and a dialkyl azodicarboxylate, such as diethyl azodicarboxylate. Typical P^b are well known in the art, such as esters and benzyl ethers (Green, T.W. and Wuts, P.G.M., *Protective Groups in Organic Synthesis*, 2nd edition, John Wiley and Sons, Inc. New York (1991)). Alternatively, where L is a reactive leaving group such as halide or sulfonate, monosulfonylated diols **102** may be treated with a base, such as sodium hydride in a solvent such as DMF and then treated with **129**. Removal of P^b is routinely accomplished using the reaction conditions well-known in the art. For example, deprotection of benzyl ethers may be effected through catalytic hydrogenation using palladium on carbon as a catalyst in solvents such as ethanol or tetrahydrofuran. Deprotection of an acetate is accomplished by basic hydrolysis, most preferably with sodium hydroxide in aqueous tetrahydrofuran. The resulting alcohol is then oxidized using routine procedures for the oxidation of alcohols (see for Example Carey F.A, Sundberg, R.J., *Advanced Organic Chemistry, Part B: Reactions and Synthesis*, 3rd edition, Plenum Press, New York (1990)) such as the Swern oxidation (Mancuso *et al.*, *Journal of Organic Chemistry*:3329 (1976)), pyridinium chlorochromate (Corey & Suggs,

Tetrahedron Letters:2647 (1975)), pyridinium dichromate (Corey & Schmidt, *Tetrahedron Letters*:399 (1979)), or sulfur trioxide-pyridine complex/dimethylsulfoxide (*Tetrahedron Letters 28*:1603 (1987)). Still alternatively, **102** may be coupled directly to **133** where L = OH or a reactive leaving group such as halide, alkyl sulfonate, or aryl sulfonate. In the case of L = OH, the Mitsunobu coupling procedure may be used. In cases where L is a reactive leaving group such as halide or sulfonate, monosulfonylated diol **102** may be treated with a base, such as sodium hydride in a solvent such as DMF and then treated with **133**.

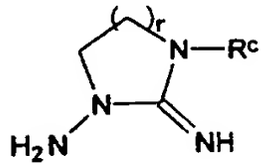
Alternatively, monosulfonylated diol **102** may be converted to **129** by the Mitsunobu coupling procedure using **133** wherein L = OH and the aldehyde or ketone is protected with a suitable protecting group, P^c. Such protecting groups are well known in the art (Green, T.W. and Wuts, P.G.M., *Protective Groups in Organic Synthesis*, 2nd edition, John Wiley and Sons, Inc. New York (1991)), and include, for example, a dimethyl ketal or acetal, 1,3-dioxalane, or 1,3-dioxane. Alternatively, where L of **133** is a reactive leaving group such as halide or sulfonate, monosulfonylated diol **102** may be treated with a base, such as sodium hydride in a solvent such as DMF and then treated with **133**. The aldehyde or ketone protecting group may then be removed to afford **129** using standard conditions well known in the art, for example, TsOH in acetone (Green, T.W. and Wuts, P.G.M., *Protective Groups in Organic Synthesis*, 2nd edition, John Wiley and Sons, Inc. New York (1991)).

Compound **129** is then treated with an aminoguanidine **130**, such as aminoguanidine or 2-hydrazinoimidazoline, optionally in the presence of an acid, such as nitric acid, hydrogen chloride, or hydrogen bromide, to afford **131**. Useful solvents include, for example, ethanol or methanol, which may contain other solvents such as methylene chloride or tetrahydrofuran.

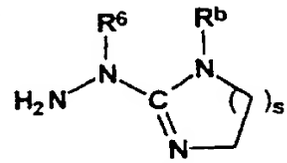
Compounds wherein R^9 and the R^7 on the carbon atom adjacent to the carbon to which R^9 is attached together form a methylene linkage can be synthesized by employing as R"L in Scheme V a cyclic ketone having a reactive

group L that is attached directly or indirectly to the carbocyclic ring. Examples of suitable reagents for R'L include 2-hydroxycyclopentanone, 3-hydroxycyclopentanone, 2-hydroxycyclohexanone and 3-hydroxycyclohexanone.

Compounds wherein R^6 and R^b of Formula *X* are taken together with the nitrogens to which they are attached to form a ring structure are prepared by substituting a heterocyclic amine **134** (below) for the aminoguanidine **130** in Scheme **V**.



134

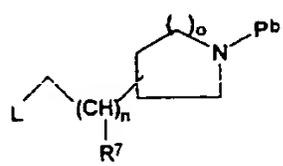


135

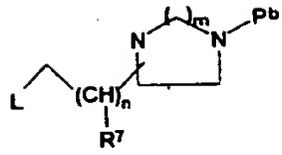
Compounds *I* wherein R^a and R^c of Formula *X* are taken together with the nitrogen atoms to which they are attached to form an imidazoline moiety are prepared by substituting a 2-hydrazinoimidazoline **135** (below) for the aminoguanidine **130** in Scheme *V*.

Schemes *Ia - V* can be followed to form other heterocyclic and heteroaryl compounds within the full scope of the invention by employing the appropriate heterocyclic starting material for each of the above schemes. Many of these starting materials are commercially available and others can be synthesized from available heterocycles using techniques that are known to those of skill in the art.

Compounds wherein W is one of Formula *VI* through *IX* can be synthesized according to Schemes *Ia - III* by substituting one of



136



137

for one of the reactive compounds **103** or **116** in the above schemes.

For medicinal use, the pharmaceutically acceptable acid addition salts, those salts in which the anion does not contribute significantly to toxicity or pharmacological activity of the organic cation, are preferred. The acid addition salts are obtained either by reaction of an organic base of Formula *I* with an organic or inorganic acid, preferably by contact in solution, or by any of the standard methods detailed in the literature available to any practitioner skilled in the art. Examples of useful organic acids are carboxylic acids such as maleic acid, acetic acid, tartaric acid, propionic acid, fumaric acid, isethionic acid, succinic acid, cyclamic acid, pivalic acid and the like; useful inorganic acids are hydrohalide acids such as HCl, HBr, HI; sulfuric acid; phosphoric acid and the like. Preferred acids for forming acid addition salts include HCl and acetic acid.

The compounds of the present invention represent a novel class of potent inhibitors of metallo, acid, thiol and serine proteases. Examples of the serine proteases inhibited by compounds within the scope of the invention include leukocyte neutrophil elastase, a proteolytic enzyme implicated in the pathogenesis of emphysema; chymotrypsin and trypsin, digestive enzymes; pancreatic elastase, and cathepsin G, a chymotrypsin-like protease also associated with leukocytes; thrombin and factor Xa, proteolytic enzymes in the blood coagulation pathway. Inhibition of thermolysin, a metalloprotease, and pepsin, an acid protease, are also contemplated uses of compounds of the present invention. The compounds of the present invention are preferably employed to inhibit trypsin-like proteases.

An end use application of the compounds that inhibit chymotrypsin and trypsin is in the treatment of pancreatitis. For their end-use application, the potency and other biochemical parameters of the enzyme-inhibiting

characteristics of the compounds of the present invention is readily ascertained by standard biochemical techniques well-known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity of the disease state of the patient or animal to be treated, as determined by the attending diagnostician. It is expected that a useful dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Compounds of the present invention that are distinguished by their ability to inhibit either factor Xa or thrombin may be employed for a number of therapeutic purposes. As factor Xa or thrombin inhibitors, compounds of the present invention inhibit thrombin production. Therefore, these compounds are useful for the treatment or prophylaxis of states characterized by abnormal venous or arterial thrombosis involving either thrombin production or action. These states include, but are not limited to, deep vein thrombosis; disseminated intravascular coagulopathy which occurs during septic shock, viral infections and cancer; myocardial infarction; stroke; coronary artery bypass; hip replacement; and thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty (PCTA). The compounds of the present invention may also be used as an anticoagulant in extracorporeal blood circuits.

By virtue of the effects of both factor Xa and thrombin on a host of cell types, such as smooth muscle cells, endothelial cells and neutrophils, the compounds of the present invention find additional use in the treatment or prophylaxis of adult respiratory distress syndrome; inflammatory responses, such as edema; reperfusion damage; atherosclerosis; and restenosis following an injury such as balloon angioplasty, atherectomy, and arterial stent placement.

The compounds of the present invention may be useful in treating neoplasia and metastasis as well as neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease.

When employed as thrombin or factor Xa inhibitors, the compounds of the present invention may be administered in an effective amount within the dosage

range of about 0.1 to about 500 mg/kg, preferably between 0.1 to 10 mg/kg body weight, on a regimen in single or 2-4 divided daily doses.

When employed as inhibitors of thrombin, the compounds of the present invention may be used in combination with thrombolytic agents such as tissue plasminogen activator, streptokinase, and urokinase. Additionally, the compounds of the present invention may be used in combination with other antithrombotic or anticoagulant drugs such as, but not limited to, fibrinogen antagonists and thromboxane receptor antagonists.

Human leucocyte elastase is released by polymorphonuclear leukocytes at sites of inflammation and thus is a contributing cause for a number of disease states. Thus, compounds of the present invention are expected to have an anti-inflammatory effect useful in the treatment of gout, rheumatoid arthritis and other inflammatory diseases, and in the treatment of emphysema. Cathepsin G has also been implicated in the disease states of arthritis, gout and emphysema, and in addition, glomerulonephritis and lung infestations caused by infections in the lung. In their end-use application the enzyme inhibitory properties of the compounds of Formula *I* is readily ascertained by standard biochemical techniques that are well-known in the art.

The neutrophil elastase inhibitory properites of compounds within the scope of the present invention are determined by the following method. Neutrophil elastase is prepared by the procedure described by Baugh *et al.*, *Biochemistry 15*: 836 (1979). Enzyme assays are conducted substantially according to the procedure disclosed by Nakajima *et al.*, *J. Biol. Chem. 254*: 4027 (1979), in assay mixtures containing 0.10 M Hepes (N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid) buffer, pH 7.5; 0.5 M NaCl; 10% dimethylsulfoxide; and 1.50×10^{-4} M MeOSuc-Ala-Ala-Pro-Val-*p*-nitroanilide as substrate. Inhibitors are evaluated by comparing enzymatic activity measured in the presence and absence of inhibitor.

The Cathepsin G inhibitory properties of compounds within the scope of the present invention are determined by the following method. A preparation of

partially purified human Cathepsin G is obtained by the procedure of Baugh *et al.*, *Biochemistry 15*: 836 (1979). Leukocyte granules are a major source for the preparation of leukocyte elastase and cathepsin G (chymotrypsin-like activity). Leukocytes are lysed and granules are isolated. The leukocyte granules are extracted with 0.20 M sodium acetate, pH 4.0, and extracts are dialyzed against 0.05 M Tris buffer, pH 8.0 containing 0.05 M NaCl overnight at 4°C. A protein fraction precipitates during dialysis and is isolated by centrifugation. This fraction contains most of the chymotrypsin-like activity of leukocyte granules. Specific substrates are prepared for each enzyme, namely MeOSuc-Ala-Ala-Pro-Val-*p*-nitroanilide and Suc-Ala-Ala-Pro-Phe-*p*-nitroanilide. The latter is not hydrolyzed by leukocyte elastase. Enzyme preparations are assayed in 2.00 mL of 0.10 M Hepes buffer, pH 7.5, containing 0.50 M NaCl, 10% dimethylsulfoxide and 0.0020 M Suc-Ala-Ala-Pro-Phe-*p*-nitroanilide as a substrate. Hydrolysis of the p-nitroanilide substrate is monitored at 405 nm and at 25°.

In Vitro Inhibition of Purified Enzymes

Reagents

All buffer salts are obtained from Sigma Chemical Company (St. Louis, MO), and were of the highest purity available. The enzyme substrates, N-benzoyl-Phe-Val-Arg-*p*-nitroanilide (Sigma B7632), N-benzoyl-Ile-Glu-Gly-Arg-*p*-nitroanilide (Sigma B2291), N-*p*-tosyl-Gly-Pro-Lys-*p*-nitroanilide (Sigma T6140), and N-succinyl-Ala-Ala-Pro-Phe-*p*-nitroanilide (Sigma S7388) can be all obtained from Sigma.

Human α-thrombin and human factor Xa can be obtained from Enzyme Research Laboratories (South Bend, Indiana). Bovine trypsin can be obtained from Sigma.

K_i Determinations

All assays are based on the ability of the test compound to inhibit the enzyme catalyzed hydrolysis of a peptide *p*-nitroanilide substrate. In a typical K_i determination, substrate is prepared in DMSO, and diluted into an assay buffer consisting of 50mM HEPES, 200 mM NaCl, pH 7.5. The final concentration for each of the substrates is listed below. In general, substrate concentrations are lower than the experimentally determined value for K_m. Test compounds are prepared as a 0.16 mg/mL solution in DMSO. Dilutions are prepared in DMSO yielding 8 final concentrations encompassing a 200-fold concentration range. Enzyme solutions are prepared at the concentrations listed below in assay buffer.

In a typical K_i determination, into each well of a 96 well plate is pipetted 280 uL of substrate solution, 10 μL of inhibitor solution, and the plate allowed to thermally equilibrate at 37°C in a Molecular Devices plate reader for >10 minutes. Reactions were initiated by the addition of a 20 μL aliquot of enzyme, and the absorbance increase at 405 nm is recorded for 15 minutes. Data corresponding to less than 10% of the total substrate hydrolysis were used in the calculations. The ratio of the velocity (rate of the change in absorbance as a function of time) for a sample containing no inhibitor is divided by the velocity of a sample containing inhibitor, and is plotted as a function of inhibitor concentration. The data are fit to a linear regression, and the value of the slope of the line calculated. The inverse of the slope is the experimentally determined K_i value.

Thrombin activity is assessed as the ability to hydrolyze the substrate Suc-Ala-Ala-Pro-Arg-*p*NA. Substrate solutions are prepared at a concentration of 20 μM (20uM<<K_m=180 μM) in assay buffer. Final DMSO concentration is 0.3%. Purified human α-thrombin is diluted into assay buffer to a concentration of 450 nM. Final reagent concentrations are: [thrombin] = 0.5 nM, [Suc-Ala-Ala-Pro-Arg-*p*NA] = 20 μM.

Factor Xa activity is assessed as the ability to hydrolyze the substrate Bz-Ile-Glu-Gly-Arg-*p*NA. Substrate solutions are prepared at a concentration of 51

μM (51 μM<<K_m=1.3 mM) in assay buffer. Final DMSO concentration is 0.3%. Purified activated human Factor Xa is diluted into assay buffer to a concentration of 300 nM. Final reagent concentrations are: [FXa] = 20 nM, [Bz-Ile-Glu-Gly-Arg-*p*NA] = 51 μM.

Trypsin activity is assessed as the ability to hydrolyze the substrate Bz-Phe-Val-Arg-*p*NA. Substrate solutions are prepared at a concentration of 14 μM (14 μM<<K_m=291 μM) in assay buffer. Final DMSO concentration is 0.3%. Purified bovine trypsin was diluted into assay buffer to a concentration of 150 nM. Final reagent concentrations are: [Trypsin] = 10 nM, [Bz-Phe-Val-Arg-*p*NA] = 14 μM.

Chymotrypsin activity is assessed as the ability to hydrolyze the substrate Suc-Ala-Ala-Pro-Phe-*p*NA. Substrate solutions are prepared at a concentration of 14 μM (14 μM<<K_m= 61uM) in assay buffer. Final DMSO concentration is 0.3%. Purified bovine α-chymotrypsin is diluted into assay buffer to a concentration of 45 nM. Final reagent concentrations are: [chymotrypsin] = 3 nM, [Suc-Ala-Ala-Pro-Phe-*p*NA] = 14 μM.

Useful dose range for the application of compounds of the present invention as neutrophil elastase inhibitors and as Cathepsin G inhibitors will of course depend upon the nature and severity of the disease state, as determined by the attending diagnostician, with the range of 0.01 to 10 mg/kg of body weight, per day, being useful for the aforementioned disease states.

Compounds of the present invention that inhibit urokinase or plasminogen activator are potentially useful in treating excessive cell growth disease state. As such the compounds of the present invention may also be useful in the treatment of benign prostatic hypertrophy and prostatic carcinoma, the treatment of psoriasis, and in their use as abortifacients. For their end-use application, the potency and other biochemical parameters of the enzyme inhibiting characteristics of the compounds of the present invention are readily ascertained by standard biochemical techniques well-known in the art. Actual dose ranges for their specific end-use application will, of course, depend upon the nature and severity

of the disease state of the patient or animal to be treated as determined by the attending diagnostician. It is to be expected that the general end-use application dose range will be about 0.01 to 10 mg per kg per day for an effective therapeutic effect.

Additional uses for compounds of the present invention include analysis of commercial reagent enzymes for active site concentration. For example, chymotrypsin is supplied as a standard reagent for use in clinical quantitation of chymotrypsin activity in pancreatic juices and feces. Such assays are diagnostic for gastrointestinal and pancreatic disorders. Pancreatic elastase is also supplied commercially as a reagent for quantitation of α_1-antitrypsin in plasma. Plasma α_1-antitrypsin increases in concentration during the course of several inflammatory diseases, and α_1-antitrypsin deficiencies are associated with increased incidence of lung disease. Compounds of the present invention can be used to enhance the accuracy and reproducibility of this assay by titrametric standardization of the commercial elastase supplied as a reagent. See, U.S. Patent No. 4,499,082.

Protease activity in certain protein extracts during purification of particular proteins is a recurring problem which can complicate and compromise the results of protein isolation procedures. Certain proteases present in such extracts can be inhibited during purification steps by compounds of the present invention, which bind tightly to various proteolytic enzymes.

The pharmaceutical compositions of the invention can be administered to any animal that can experience the beneficial effects of the compounds of the invention. Foremost among such animals are humans, although the invention is not intended to be so limited.

The pharmaceutical compositions of the present invention can be administered by any means that achieve their intended purpose. For example, administration can be by parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, buccal, or ocular routes. Alternatively, or concurrently, administration can be by the oral route. The dosage administered

will be dependent upon the age, health, and weight of the recipient, kind of concurrent treatment, if any, frequency of treatment, and the nature of the effect desired.

In addition to the pharmacologically active compounds, the new pharmaceutical preparations can contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically.

The pharmaceutical preparations of the present invention are manufactured in a manner that is, itself, known, for example, by means of conventional mixing, granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding the resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients are, in particular, fillers such as saccharides, for example, lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example, tricalcium phosphate or calcium hydrogen phosphate, as well as binders, such as, starch paste, using, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents can be added, such as, the above-mentioned starches and also carboxymethyl-starch, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as, sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as, magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings that, if desired, are resistant to gastric juices. For this purpose, concentrated saccharide solutions can be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol, and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to

produce coatings resistant to gastric juices, solutions of suitable cellulose preparations, such as, acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments can be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

Other pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as, glycerol or sorbitol. The push-fit capsules can contain the active compounds in the form of granules that may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as, fatty oils or liquid paraffin. In addition, stabilizers may be added.

Suitable formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form, for example, water-soluble salts, alkaline solutions and cyclodextrin inclusion complexes. Especially preferred alkaline salts are ammonium salts prepared, for example, with Tris, choline hydroxide, Bis-Tris propane, N-methylglucamine, or arginine. One or more modified or unmodified cyclodextrins can be employed to stabilize and increase the water solubility of compounds of the present invention. Useful cyclodextrins for this purpose are disclosed in U.S. Patent Nos. 4,727,064, 4,764,604, and 5,024,998.

In addition, suspensions of the active compounds as appropriate oily injection suspensions can be administered. Suitable lipophilic solvents or vehicles include fatty oils, for example, sesame oil, or synthetic fatty acid esters, for example, ethyl oleate or triglycerides or polyethylene glycol-400 (the compounds are soluble in PEG-400). Aqueous injection suspensions can contain substances that increase the viscosity of the suspension, for example, sodium carboxymethyl cellulose, sorbitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

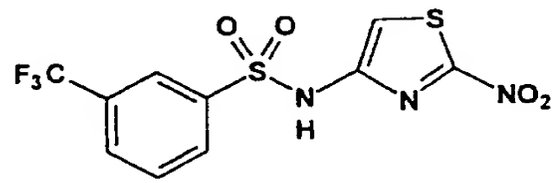
The following examples are illustrative, but not limiting, of the method and compositions of the present invention. Other suitable modifications and adaptations of the variety of conditions and parameters normally encountered and obvious to those skilled in the art are within the spirit and scope of the invention.

Examples

Example 1

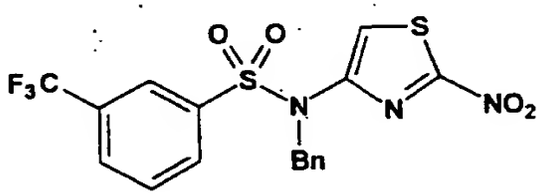
Preparation of N-benzyl-N-[2-(5-(3-amidinophenyl)methylamino)thiazolyl] benzenesulfonamide hydrochloride salt

a) N-[2-(5-Nitrothiazolyl)]benzenesulfonamide



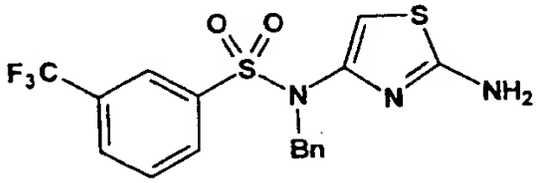
To 50 mmol of 2-amino-5-nitrothiazole (Aldrich) and 55 mmol of 4-methylmorpholine in 200 mL of anhydrous methylene chloride is added 50 mmol of 3-(triflouromethyl)benzenesulfonyl chloride (Aldrich). The mixture is stirred under nitrogen for 24 h and then washed with saturated $NaHCO_3$ (2 x 200 mL), brine (200 mL) and dried (Na_2SO_4). The solution is concentrated and the resulting residue is chromatographed on silica gel to afford the title compound.

b) N-Benzyl-N-[2-(5-nitrothiazolyl)]benzenesulfonamide



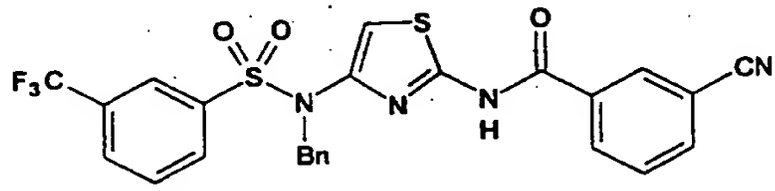
To 25.0 mmol of N-[2(5-nitrothiazolyl)]benezenesulfonamide, as prepared in the preceding step, in 50 mL of anhydrous N,N-dimethylformamide under nitrogen is added 37.5 mmol of powdered anhydrous potassium carbonate and 27.5 mmol of benzyl bromide. After stirring for 2-12 h, the mixture is partitioned between 250 mL of ethyl acetate and 250 mL of water. The aqueous layer is extracted with 100 mL of ethyl acetate and the combined organic phases are washed with 1 M K_2CO_3 (2 x 100 mL, water (3 x 150 mL) and brine (150 mL). The solution is dried (Na_2SO_4) and concentrated to give the title compound after silica gel chromatography.

c) N-Benzyl-N-[2-(5-nitrothiazolyl)]benzenesulfonamide



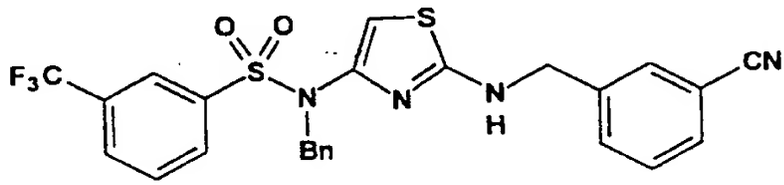
To 10.0 mmol of N-benzyl-N-[2-(5-nitrothiazolyl)]benzenesulfonamide, as prepared in the preceding step, in 100 mL of methanol-THF (1:1) is added 500 mg of 10% palladium on carbon. After stirring the mixture under a balloon of hydrogen for 1-20 h, the mixture is filtered (CELITE, diatomaceous earth) and concentrated to afford the title compound.

d) N-Benzyl-N-[2-(5-(3-cyanobenzamido)thiazolyl)]benzenesulfonamide



To 4.0 mmol of 3-cyanobenzoic acid and 4.0 mmol of Castro's Reagent (benzotriazole-1-yloxytris(dimethylaminophosphonium hexafluorophosphate, BOP) in 10 mL of anhydrous N,N-dimethylformamide (DMF) is added 6.0 mmol of N,N-diisopropylethylamine and the mixture is stirred under nitrogen for 5 min. A solution of 3.8 mmol of N-benzyl-N-[2-(5-aminothiazolyl)] benzenesulfonamide, as prepared in the preceding step, in 4 mL of DMF is added. After stirring for 20 h, 30 mL of saturated $NaHCO_3$ is added. The mixture is partitioned between 100 mL each of ethyl acetate and water. The organic layer is washed with saturated $NaHCO_3$ (2 x 60 mL), brine (100 mL) and dried (Na_2SO_4). Concentration and chromatography on silica gel affords the title compound.

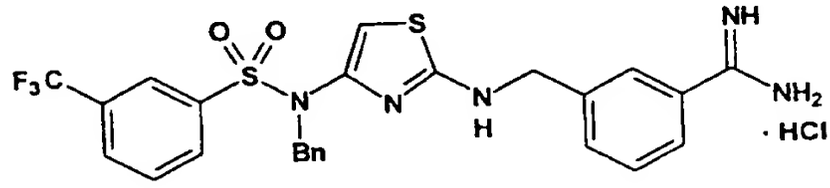
e) N-Benzyl-N-[2-(5-(3-cyanophenyl)methylamino)thiazolyl)] benzenesulfonamide



To 6.0 mmol of 2 M lithium borohydride in THF is added 8 mL of anhydrous THF followed by 12 mmol of chlorotrimethylsilane. After stirring for 5 min, 2.0 mmol of N-benzyl-N-[2-(5-(3-cyanobenzamido)thiazolyl)] benzenesulfonamide, as prepared in the preceding step, in 50 mL of THF is added and the mixture is heated to 50 °C under nitrogen for 2 h. After quenching the reaction with 1.2 mL of MeOH, 8 mL of 2 N NaOH is added, the mixture stirred

for 10 min and then extracted with ethyl acetate (2 x 60 mL). The combined extracts are washed with brine, dried (Na_2SO_4) and concentrated. Chromatography silica gel of the resulting residue affords the title compound.

f) N-Benzyl-N-[2-(5-(3-amidinophenyl)methylamino)thiazolyl)] benzenesulfonamide hydrochloride salt

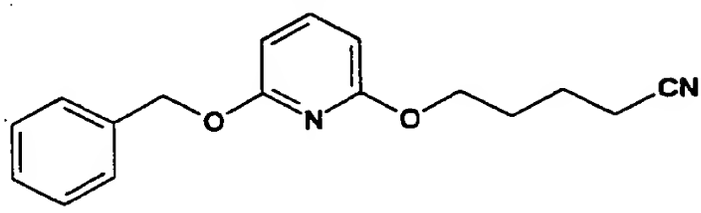


To a solution of 1.0 mmol of N-benzyl-N-[2-(5-(3-cyanophenyl) methylamino)thiazolyl)]benzenesulfonamide, as prepared in the preceding step, in methylene chloride (10 mL) is added 37% HCl in ethanol (20 mL) at 0°C. The mixture is stirred at room temperature for 2 days, the solvent evaporated and the residue co-evaporated with methylene chloride several times. The residue is dissolved in ethanol (20 mL), ammonium carbonate (4.0 mmol) is added at 0°C and the mixture is stirred at room temperature overnight. Methylene chloride (150 mL) is added to the mixture and the mixture is washed with 10% K_2CO_3 (2 x 50 mL) and dried (K_2CO_3). The solution is concentrated and the residue is treated with 2.0 mL of 1 M HCl in 10 mL of THF and concentrated again. The residue is then purified by crystallization to give the title compound.

Example 2

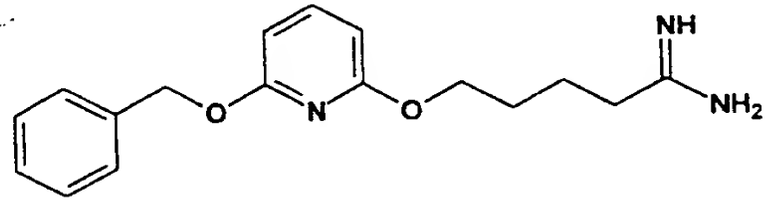
Preparation of 2-Benzyloxy-6-(4-amidinobutoxy)pyridine

a) 2-Benzyloxy-6-(4-cyanobutoxy)pyridine



To 7.96 mmol of 6-phenylmethoxy-(1H)-pyridinone (C. Kaneko *et al.*, *J. Chem. Soc., Chem. Commun.*, 1177-1181 (1980)) in N-N-dimethylformamide (3 mL) at 0°C is added 8.33 mmol of sodium hydride (100%) and the reaction mixture is stirred for 5 min. To the reaction mixture is added 10.1 mmol of 5-bromovaleronitrile. The reaction mixture is stirred in ambient temperature overnight, quenched with 1 N hydrochloric acid and extracted into diethyl ether. The solution is dried ($MgSO_4$), and purified by flash chromatography on silica gel.

b) 2-Benzyloxy-6-(4-amidinobutoxy)pyridine

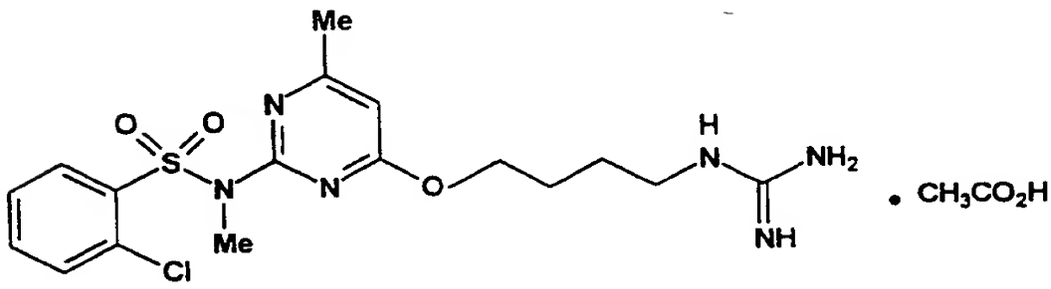


A solution of 0.5 mmol 2-benzyloxy-6-(4-cyanobutoxy)pyridine in 10 mL of 37% HCl in ethanol is stirred at 0°C overnight. The reaction is concentrated to dryness, diluted with ethanol (5 mL) and treated with 20 equivalents of ammonium carbonate. The reaction mixture is then stirred for 40 min. The reaction mixture is quenched with 2 N sodium hydroxide, extracted into

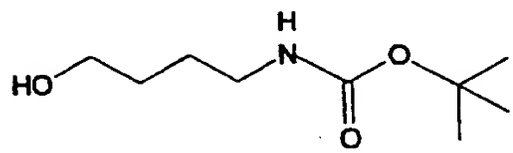
methylene chloride, dried (K_2CO_3), and concentrated to dryness to provide the title compound.

Example 3

4-[4-Amino(imino)methylaminobutoxy]-6-methyl-2-[N-methyl-2-(chlorophenylsulfonamido)]pyrimidine acetate



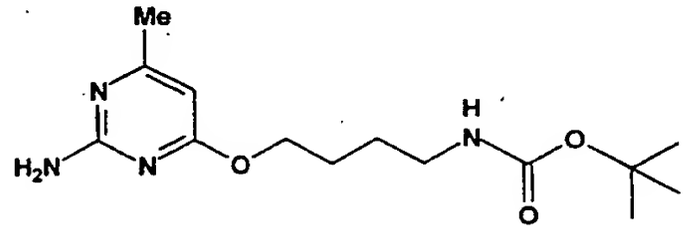
a) t-Butyl N-(4-hydroxybutyl)carbamate



To a cooled (0°C) solution of 0.250 mol of di-*t*-butyl dicarbonate (Aldrich Chemical Company) and 0.300 mol of *N,N*-diisopropylethylamine in 120 mL anhydrous tetrahydrofuran is added 0.250 mol of 4-amino-1-butanol (Aldrich Chemical Company) in 30 mL of tetrahydrofuran. After stirring at ambient temperature under nitrogen for 2 h, the mixture is concentrated *in vacuo* to remove the majority of solvent. 300 mL of ethyl acetate is added and the mixture washed with 3x300 mL of water, 2x300 mL of 1N HCl, 300 mL of saturated

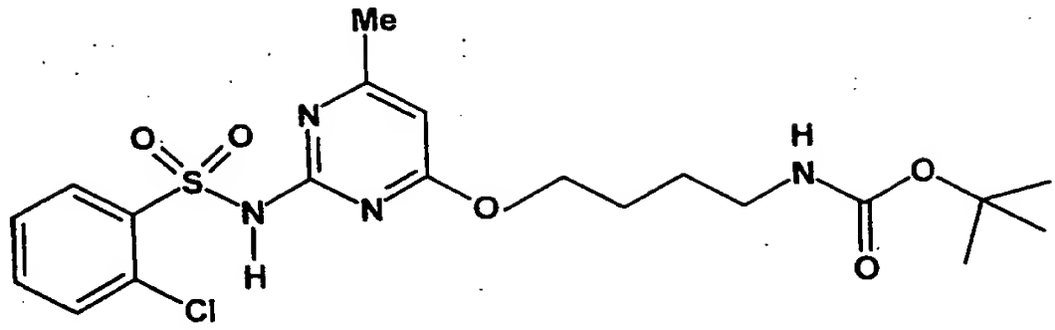
$NaHCO_3$, 300 mL of brine, dried (Na_2SO_4) and concentrated to afford the title compound.

b) t-Butyl N-[4-(2-amino-6-methylpyrimidin-4-yloxy)]butylcarbamate



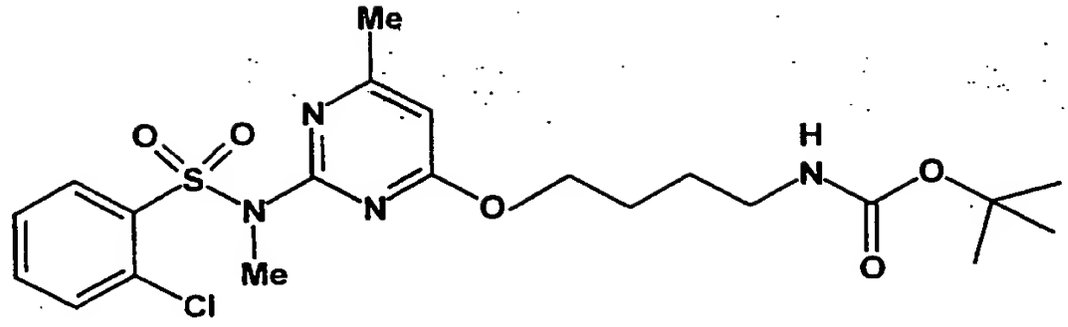
To a cooled (0°C) suspension of 40 mmol of dry sodium hydride in 20 mL of anhydrous *N,N*-dimethylformamide under nitrogen is added dropwise a solution of 42 mmol *t*-butyl *N,N*-dimethylformamide. After stirring for 30 min, 40 mmol of 2-amino-4-chloro-6-methylpyrimidine (Aldrich Chemical Company) in 35 mL *N,N*-dimethylformamide is added and the mixture stirred at ambient temperature for 3 h. The mixture is carefully quenched with 25 mL of 10 wt % aqueous citric acid and the mixture concentrated to near dryness under high vacuum. The combined organic layers are then washed with 250 mL of brine, dried (Na_2SO_4) and concentrated and the resulting residue is chromatographed on silica gel to afford the title compound.

c) t-Butyl N-[4-[2-(2-chlorophenylsulfonamido)-6-methylpyrimidin-4-yloxy)]butylcarbamate



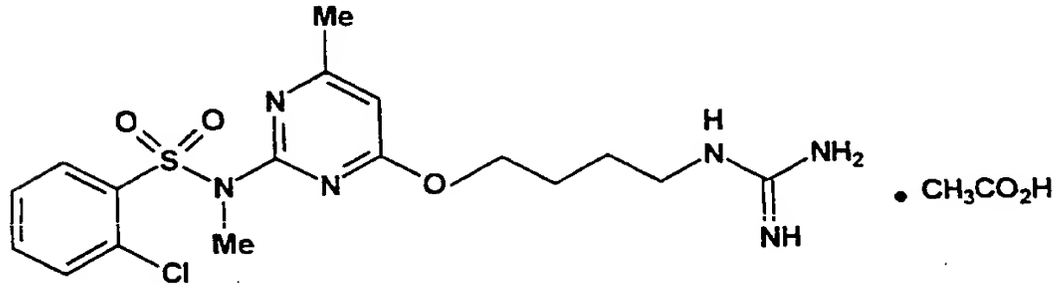
To 20 mmol of *t*-butyl *N*-[4-(2-amino-6-methylpyrimidin-4-yloxy)]butylcarbamate, as prepared in the preceding step and 24 mmol of *N,N*-diisopropylethylamine in 100 mL of anhydrous tetrahydrofuran is added 21 mmol of 2-chlorobenzenesulfonyl chloride (Lancaster Synthesis, Inc.) dropwise over 5 min. After stirring at ambient temperature for 2 h, the reaction mixture is concentrated. The residue is partitioned between 250 mL of ethyl acetate and 250 mL of water. The organic layer is then washed with 250 mL of brine, dried (Na_2SO_4) and concentrated and the resulting residue is chromatographed on silica gel to afford the title compound.

d) t-Butyl N-[4-[2-(N-methyl-2-chlorophenylsulfonamido)-6-methylpyrimidin-4-yloxy)]butylcarbamate



To 10.0 mmol of *t*-butyl N-[4-[2-(N-methyl-2-chlorophenylsulfonamido)-6-methylpyrimidin-4-yloxy)]butylcarbamate, as prepared in the preceding in 30 mL of anhydrous *N,N*-dimethylformamide is added 11.0 mmol iodomethane and 20.0 mmol of anhydrous potassium carbonate. After stirring at ambient temperature for 1 h, the reaction mixture is partitioned between 150 mL of ethyl acetate and 150 mL of water. The organic layer is then washed with 150 mL of water, 150 mL of saturated aq. $NaHCO_3$ and 200 mL of brine and then dried (Na_2SO_4) and concentrated. The resulting residue is chromatographed on silica gel to afford the title compound.

e) 4-[4-Amino(imino)methylaminobutoxy]-6-methyl-2-[N-methyl-2-(chlorophenylsulfonamido)]pyrimidine acetate



t-Butyl *N*-4[4-[2-(*N*-methyl-2-chlorophenylsulfonamido)-6-methylpyrimidin-4-yloxy)]-butylcarbamate (2.00 mmol), as prepared in the preceding step, is treated with 20 mL of 4N HCl in dioxane and the mixture stirred at ambient temperature for 3 h. The mixture is concentrated and the residue concentrated twice more from 20 mL portions of chloroform to afford the amine salt. This residue is dissolved in 25 mL of anhydrous *N,N*-dimethylformamide and treated with 3.00 mmol of *N,N*-diisopropylethylamine and 4.00 mmol of aminoiminomethanesulfonic acid and stirred 24 h. The solvent is removed *in vacuo* and the residue dissolved in 150 mL of dichloromethane, washed with 3x100 mL of 1M K_2CO_3, dried over anhydrous K_2CO_3 and concentrated. The resulting residue is chromatographed on silica gel with a methanol-dichloromethane solvent system containing 1-2% acetic acid to afford the title compound.

Having now fully described this invention, it will be understood to those of ordinary skill in the art that the same can be performed within a wide and equivalent range of conditions, formulations, and other parameters without affecting the scope of the invention or any embodiment thereof. All patents and publications cited herein are fully incorporated by reference herein in their entirety.

What Is Claimed Is:

1. A compound having the the general formula *I*:

$$R^1—Z—X—Y—W \qquad I$$

or solvates, hydrates or pharmaceutically acceptable salts thereof;

wherein:

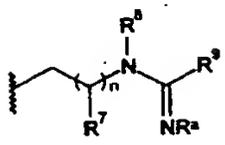
R^1 is one of alkyl, cycloalkyl, alkenyl, alkynyl, aryl, aralkyl or heteroaryl, any of which may be optionally substituted;

Z is one of $–NR^{10}SO_2–$, $–SO_2NR^{10}–$, $–NR^{10}C(R^yR^z)–$, $–C(R^yR^z)NR^{10}–$, $–OSO_2–$, $–SO_2O–$, $–OC(R^yR^z)–$, $–C(R^yR^z)O–$, $–NR^{10}CO–$ or $–CONR^{10}–$, where R^y and R^z are each independently one of hydrogen, alkyl, cycloalkyl, aryl, aralkyl, hydroxyalkyl, carboxyalkyl, aminoalkyl, monoalkylaminoalkyl, dialkylaminoalkyl or carboxy, and R^{10} is defined below;

X is a stable 5- to 7-membered monocyclic or 7- to 10-membered bicyclic heterocyclic moiety that is either saturated or unsaturated, and which consists of carbon atoms and from 1 to 4 heteroatoms is independently selected from the group consisting of N, O and S, wherein the nitrogen and sulfur heteroatoms can optionally be oxidized, the nitrogen can optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring, and wherein the heterocyclic ring can be attached to pendant groups Y and Z at any heteroatom or carbon atom that results in a stable formula; and wherein the heterocyclic ring can be optionally substituted on carbon or on a nitrogen atom if the resulting compound is stable;

Y is one of $-O–$, $-NR^{10}–$, $-S–$, $-CHR^{10}–$ or a covalent bond;

W is one of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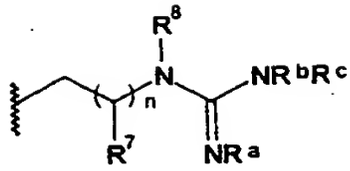
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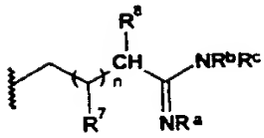
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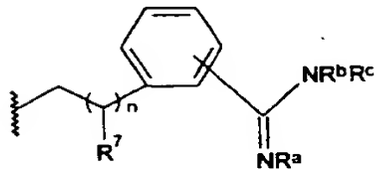
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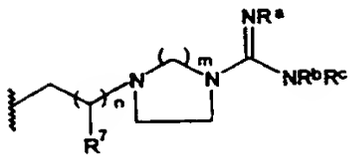
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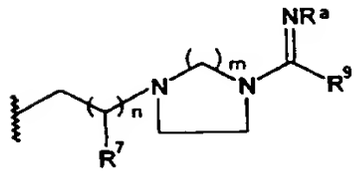
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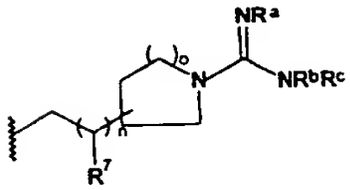
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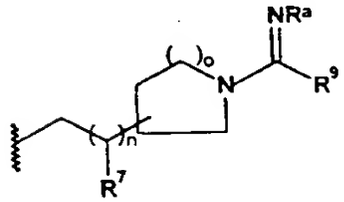
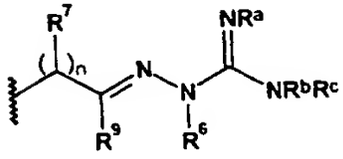

IX,


X,

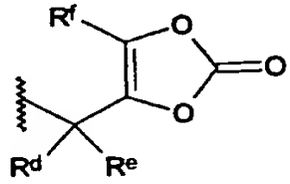
R^6 is one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl, aminoalkyl, monoalkylamino(C_{2-10})alkyl, dialkylamino(C_{2-10})alkyl, carboxyalkyl or $-CO_2R^w$, where R^w is defined below;

R^7 and R^8 are each independently one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl or carboxyalkyl;

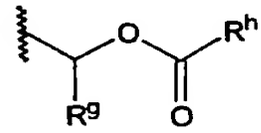
R^9 is one of hydrogen, alkyl, cycloalkyl or aryl, wherein said alkyl, cycloalkyl or aryl can be optionally substituted with amino, monoalkylamino, dialkylamino, alkoxy, hydroxy, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, aryl, heteroaryl, acylamino, cyano or trifluoromethyl;

R^{10}, in each instance, is independently one of hydrogen, alkyl, aralkyl, aryl, hydroxyalkyl, aminoalkyl, monoalkylamino(C_{2-10})alkyl, dialkylamino(C_{2-10})alkyl, alkoxycarbonylalkyl or carboxyalkyl;

R^a, R^b and R^c are each independently one of hydrogen, alkyl, hydroxy, alkoxy, aryloxy, aralkoxy, alkoxycarbonyloxy, cyano or $-CO_2R^w$, where R^w is alkyl, cycloalkyl, phenyl benzyl,



or



where R^d and R^e are independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or phenyl, R^f is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or phenyl, R^g is hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl or phenyl, and R^h is aralkyl or C_{1-6} alkyl;

n is from zero to 8;

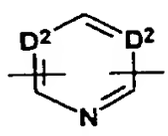
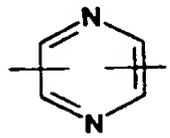
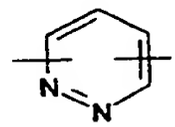
o is from zero to 4; and

m is from 2 to 4.

2. A compound of claim 1, wherein:

R^1 is one of C_{6-10} aryl, pyridinyl, quinizolinyl, quinolinyl or tetrahydroquinolinyl, any of which is optionally substituted by one or two of hydroxy, nitro, trifluoromethyl, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} aminoalkyl, C_{1-6} aminoalkoxy, amino, mono(C_{1-4})alkylamino, di(C_{1-4})alkylamino, C_{2-6} alkoxycarbonylamino, C_{2-6} alkoxycarbonyl, carboxy, C_{1-6} hydroxyalkyl, C_{2-6} hydroxyalkoxy, C_{2-10} mono(carboxyalkyl)amino, di(C_{2-10} carboxyalkyl)amino, C_{6-14} ar(C_{1-6}) alkoxycarbonyl, C_{2-6} alkynylcarbonyl, C_{1-6} alkylsulfonyl, C_{2-6} alkenylsulfonyl, C_{2-6} alkynylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonamido, amidino, guanidino, C_{1-6} alkyliminoamino, formyliminoamino, C_{2-6} carboxyalkoxy, C_{2-6} carboxyalkyl, carboxyalkylamino, cyano, trifluoromethoxy, and perfluoroethoxy;

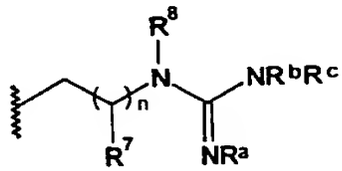
Z is one of $-SO_2O-$, $-SO_2NR^{10}-$, $-C(R^yR^z)O-$ or $-OC(R^yR^z)-$, where R^y and R^z are each hydrogen;

X is one of  ,  , or  ;

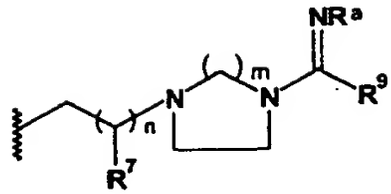
(12) (13) (14)

wherein each D^2 is independently N; $N^+(O^-)$ or CH;

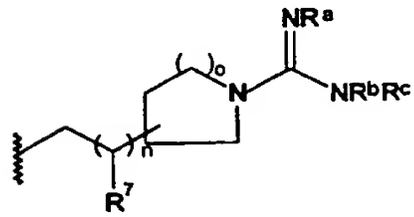
W is one of



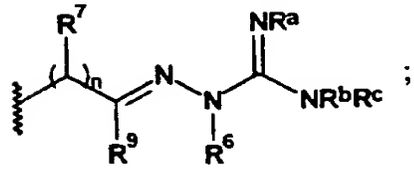
III



VII



VIII or



; *X*

Y is one of –O–, –S–, –NR^{10}–, or a covalent bond;

R^6 is one of hydrogen, C_{1-6} alkyl, C_{6-10} ar(C_{1-6})alkyl, C_{6-10} aryl, C_{2-10} hydroxyalkyl, C_{2-10} aminoalkyl, mono(C_{1-4})alkylamino(C_{2-8})alkyl, di(C_{1-4})alkylamino(C_{2-8})alkyl or C_{2-10} carboxyalkyl;

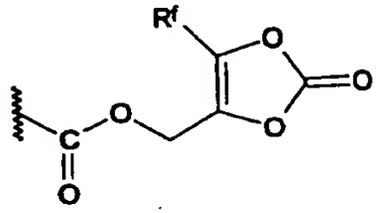
R^7 is one of hydrogen, C_{1-6} alkyl, C_{2-10} carboxyalkyl or C_{2-10} hydroxyalkyl;

R^8 is one of hydrogen, C_{1-6} alkyl, C_{2-10} carboxyalkyl or C_{2-10} hydroxyalkyl;

R^9 is hydrogen; or C_{1-10} alkyl, optionally substituted with amino, mono(C_{1-4})alkylamino, C_{1-6} alkoxy, hydroxy, carboxy, phenyl, alkyloxycarbonyl, aralkoxycarbonyl, C_{1-6} acylamino, cyano or trifluoromethyl;

R^{10}, in each instance, is independently hydrogen, C_{1-6} alkyl, benzyl, phenyl, C_{2-10} hydroxyalkyl, C_{2-10} aminoalkyl, C_{1-4} monoalkylamino(C_{2-8})alkyl, C_{1-4} dialkylamino(C_{2-8})alkyl or C_{2-10} carboxyalkyl;

R^a, R^b and R^c are each independently one of hydrogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy, phenoxy, C_{1-4} alkyloxycarbonyl, benzyloxycarbonyl, cyano,



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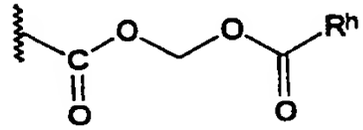


where R^h is benzyl, methyl, ethyl, isopropyl, *sec*-butyl or *t*-butyl, and where R^f is hydrogen or C_{1-6} alkyl;

n is from zero to 8;

o is from zero to 4; and

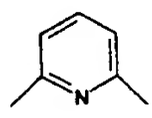
m is from 2 to 4.

3. A compound of claim 1, wherein:

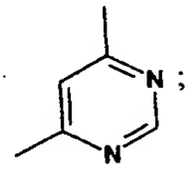
R^1 is one of C_{1-8} alkyl, phenyl or naphthyl, optionally substituted by one or two of chloro, methoxy, trifluoromethyl, amino or dimethylamino;

Z is one of $-SO_2O-$, $-SO_2NR^{10}-$, $-CH_2O-$ or $-OCH_2-$;

X is one of



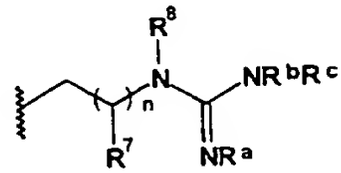
or



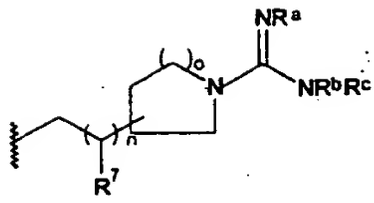
;

Y is one of O, NR^{10} or a covalent bond;

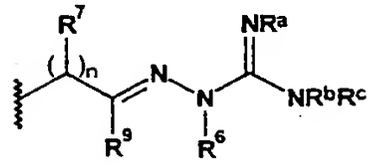
W is one of:



III;



VIII and



X

R^5 is one of hydrogen, C_{1-6} alkyl, C_{2-10} hydroxyalkyl or C_{2-10} carboxyalkyl;

R^6 is hydrogen, C_{1-4} alkyl, C_{2-4} hydroxyalkyl, C_{2-4} carboxyalkyl, C_{2-4} aminoalkyl, dimethylamino(C_{2-8})alkyl, or methylamino(C_{2-8})alkyl;

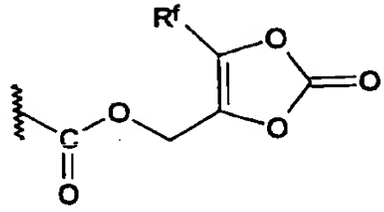
R^7 is one of hydrogen, C_{1-6} alkyl, C_{2-10} hydroxyalkyl or C_{2-10} carboxyalkyl;

R^8 is one of hydrogen, C_{1-6} alkyl, C_{2-10} hydroxyalkyl or C_{2-10} carboxyalkyl;

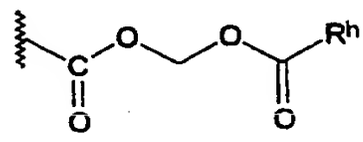
R^9 is one of hydrogen or C_{1-4} alkyl;

R^{10}, in each instance, is independently one of hydrogen, C_{1-4} alkyl, C_{2-4} hydroxyalkyl, C_{2-4} carboxyalkyl, C_{2-4} aminoalkyl, dimethylamino(C_{2-8})alkyl, methylamino(C_{2-8})alkyl;

R^a, R^b and R^c are hydrogen, hydroxy,



or



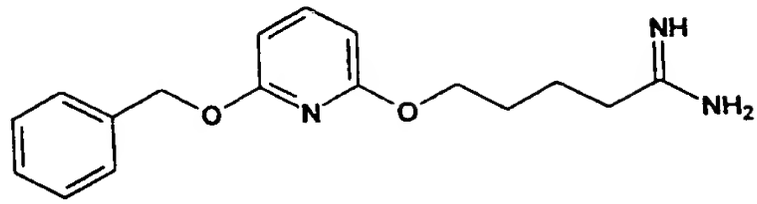
where R^h is benzyl or *t*-butyl, and where R^f is hydrogen or methyl;

n is from zero to 4;

o is 0, 1 or 2; and

m is 2 or 3.

4. A compound of claim 1, which is one of:



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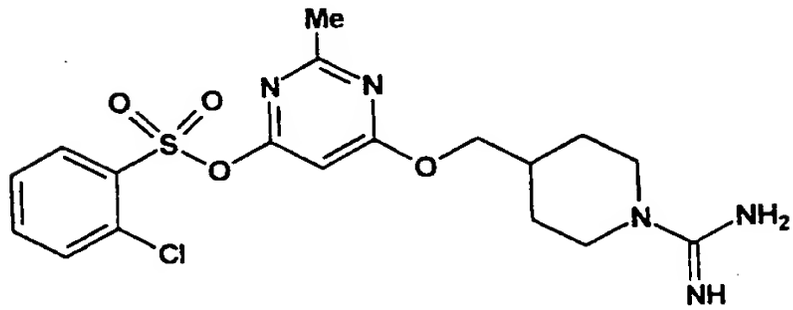
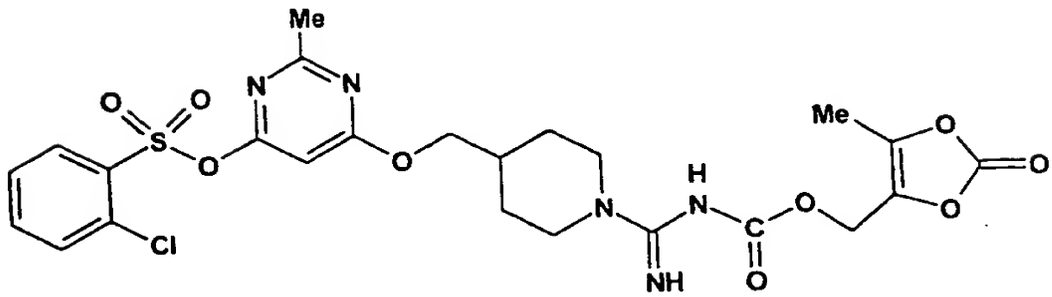
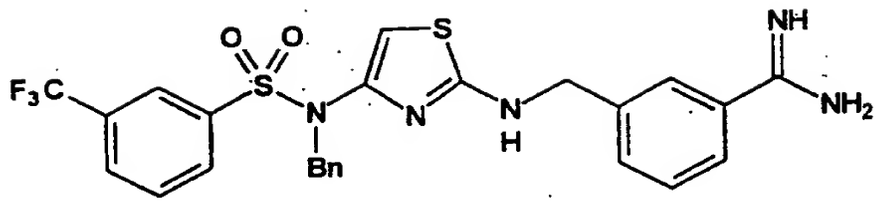
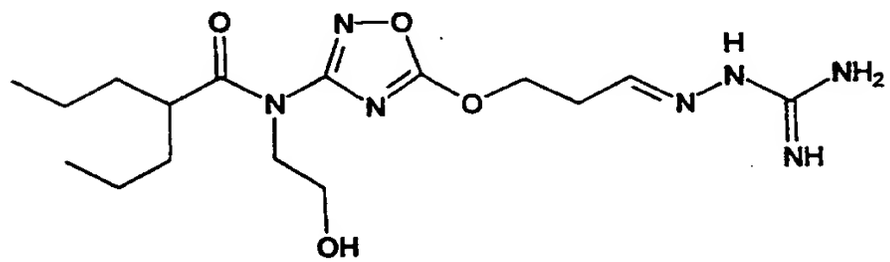
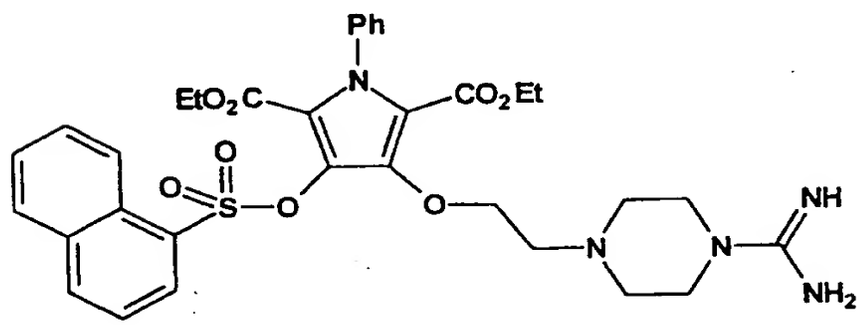






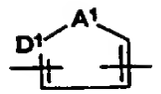




as well as pharmaceutically acceptable salts thereof.

5. A compound of claim 1, wherein:

X is one of the following heteroaryl groups having five ring atoms:



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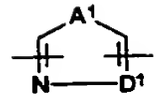
(1)



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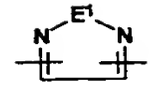
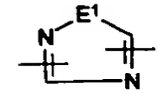
(2)



(3)

or

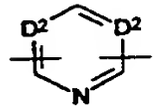


(4)

wherein A^1 is O; S or N(R), wherein R is hydrogen or C_{1-6} alkyl; D^1 is N or CH; and E^1 is O or S.

6. A compound of claim 1, wherein:

X is one of the following heteroaryl groups having six ring atoms:



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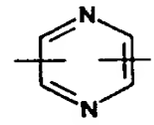
(12)



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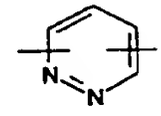
(13)



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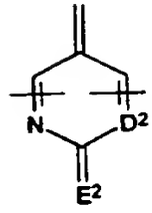
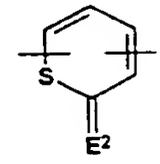
(14)



(15)

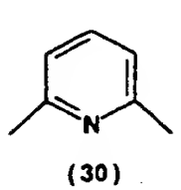
or



(16)

wherein D^2 is N; $N^+(O^-)$ or CH; and E^2 is O or S.

7. A compound of claim 1, wherein X is is selected from the group consisting of: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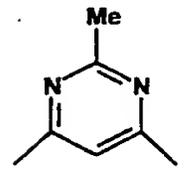
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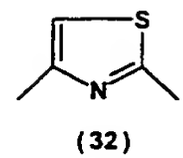
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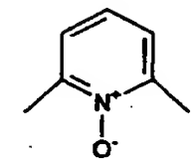
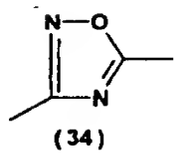

(33)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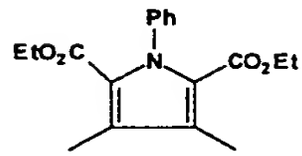
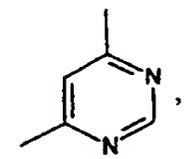

(35)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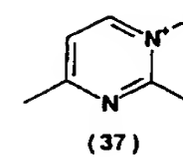
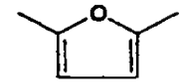

(37)


(38)

and


(39)

8. A compound of claim 1, wherein X is selected from the group consisting of 2,3-pyridyl, 2,4-pyridyl, 2,5-pyridyl, 2,6-pyridyl, 2,4-furanyl, 3,4-furanyl, 2,5-furanyl, 4,5-pyrimidinyl and 4,6-pyrimidinyl.

9. A pharmaceutical composition for inhibiting proteolysis in a mammal, comprising an amount of a compound of any one of claims 1-8 effective to inhibit proteolysis.

10. The pharmaceutical composition of claim 9 further comprising a pharmaceutically acceptable carrier or diluent.

11. The pharmaceutical composition of claim 9, comprising an amount of a compound of any one of claims 1-8 effective to inhibit a trypsin-like protease.

12. A method of inhibiting proteolysis in a mammal, comprising administering to the mammal a composition of claim 9

13. The method of claim 12. wherein a trypsin-like protease is inhibited.

14. A method of treating pancreatitis, thrombosis, ischemia, stroke, restenosis, emphysema or inflammation in a mammal, comprising administering to the mammal a composition of claim 9.

15. A method of inhibiting thrombin-induced platelet aggregation and clotting of fibrinogen in plasma, comprising administering to the mammal a composition of claim 9.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/09846

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,129,941 A (LOHER et al.) 14 July 1992, column 1, formula (I), lines 20-65.	1-15
A	US 5,021,578 A (KOCH et al.) 04 June 1991, columns 1 and 2, the entire document.	1-15
A	US 5,314,891 A (EDWARDS et al.) 24 May 1994, col. 23, see claim 1.	1-15
A	US 5,104,889 A (KANAI et al.) 14 April 1992, column 1, formula 1.	1-15
A	US 4,954,164 A (SUZUKI et al.) 04 September 1990, column 1, formula (I).	1-15

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
26 AUGUST 1997

Date of mailing of the international search report
28 OCT 1997

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
Y.N. GUPTA acc

Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/09846

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
1-15

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/09846

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K; 31/40, 31/415, 31/42, 31/425, 31/44, 31/50, 31/505, 31/495; C07D 207/36, 213/69, 237/14, 237/16, 239/47, 239/48, 239/52, 241/14, 241/18, 241/20, 251/30, 251/42, 251/48, 271/07, 277/34, 277/38

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

544/219, 240, 319, 321, 326, 327, 372, 382, 383, 384, 385; 546/276.4, 278.4, 296, 304; 548/132, 133, 182, 183, 190, 191, 192, 316.4, 316.7, 317.1, 335.1, 544

B. FIELDS SEARCHED
Minimum documentation searched
Classification System: U.S.

544/219, 240, 319, 321, 326, 327, 372, 382, 383, 384, 385; 546/276.4, 278.4, 296, 304; 548/132, 133, 182, 183, 190, 191, 192, 316.4, 316.7, 317.1, 335.1, 544

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I Claims 1, 4, 5, 7 and 9-15, drawn to compound, composition and method of use when X is a five membered hetero ring.

Group II Claims 1-4 and 6-15, drawn to compound, composition and method of use when X is six membered hetero ring containing only one nitrogen atom.

Group III Claims 1-4 and 6-15, drawn to compound, composition and method of use when X is six membered hetero ring containing more than one nitrogen atoms.

Group IV Claims 1 and 9-15, drawn to compound, composition and method of use when X is seven membered hetero ring.

Group V Claims 1 and 9-15, drawn to compound, composition and method of use when X is any compound other than compounds of Groups I-IV.

The inventions listed on Groups I-V do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The inventions of Groups I-V are drawn to structurally dissimilar compounds. They are made and used independently. They are independent. The compounds thiazoles, oxazoles, diazoles and oxadiazoles of Group I, are different products than the compounds of Groups II-V because pyridines of Group II, diazines of Group III azepines of Group IV and oxazines, thiazines, oxadiazines and other heterocyclic compounds of Group V are structurally different. Therefore, they do not share a common special technical feature which is not a special technical feature by definition and, thus, Groups lack unity.